THE RELATIVE BURDEN OF COMORBIDITIES IN BREAST CANCER SURVIVORS: RESULTS FROM THE CLUE II AND BOSS COHORTS

by

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Abstract

Advances in screening and treatment strategies have led to a growing population of long-term breast cancer survivors in the United States. Although studies in breast cancer survivors have reported bone loss, cardiovascular disease (CVD), and trends in mortality, the additional effect of cancer and its treatment on these outcomes is unclear due to limited comparisons with cancer-free women. The aim of this dissertation was to evaluate the risk of bone loss, CVD, and mortality in breast cancer survivors relative to a cancer-free comparison within the same cohort.

First, we prospectively examined all-cause and CVD-related mortality in breast cancer survivors relative to cancer-free women in a community-based cohort. We found that survivors, irrespective of stage, estrogen-receptor (ER)-status, and time since diagnosis, had a higher risk of all-cause mortality compared to cancer-free women. We further observed an increase in all-cause mortality over time among survivors diagnosed at age ≥70. Survivors had higher CVD-related mortality after 8 years, particularly among those diagnosed at age ≥70 and those with ER-positive tumors, compared to cancer-free women.

Second, we examined incident CVD risk factors shortly after diagnosis in breast cancer survivors compared to cancer-free women within a familial risk cohort. Overall, survivors did not have a higher risk of hypertension, high cholesterol, or diabetes compared to cancer-free women. However, compared to cancer-free women, survivors had an increased risk of high triglycerides and survivors diagnosed at age ≤50 years had an increased risk of hypertension.

Third, we prospectively evaluated bone loss in breast cancer survivors compared to cancer-free women within a familial risk cohort. We found an overall increased risk of bone loss in survivors compared to cancer-free women. Risk of bone loss was higher among women diagnosed at age ≤50 years, women with ER-positive tumors, and women treated with aromatase inhibitors alone or chemotherapy plus any hormonal therapy.

Overall, this dissertation informs and improves our understanding of breast cancer and its related treatment on bone loss, CVD, and mortality. Results support a more tailored approach to treatment and prevention strategies, and further evaluation of these interventions to improve the long-term survival in breast cancer survivors.

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Chapter 1. Introduction

Overview

This dissertation examines both short- and long-term adverse health outcomes among breast cancer survivors compared to cancer-free women. Observational and clinical studies have reported that breast cancer survivors have an increased risk of bone loss, cardiovascular disease (CVD), and overall mortality. However, it is unclear if these adverse outcomes are primarily due to the effects of breast cancer and its treatment or may be driven, in part, by age, menopause, and lifestyle factors. Thus, the overarching aim of this dissertation is to determine whether the risk of these adverse outcomes is higher in breast cancer survivors relative to cancer-free women of similar age.

This dissertation aims to address the following questions: Are breast cancer survivors at increased risk for long-term all-cause and CVD-related mortality compared to cancer-free women and does this risk vary by tumor characteristics, age at diagnosis, and time since diagnosis? Do breast cancer survivors have a higher risk of developing CVD risk factors shortly after diagnosis compared to their cancer-free peers? Are young women with breast cancer at increased risk for bone loss after diagnosis compared to cancer-free women?

The answers to these questions will help inform additional health risks specific to survivors, which may be due to breast cancer and its treatment versus factors such as age, menopause, and lifestyle that apply to all women. This information can then be used to guide the evaluation of interventions to reduce the risk of bone loss and CVD as well as improve the long-term survival in breast cancer survivors.

Background

1-1. Breast cancer incidence

In the United States, breast cancer is the most common cancer (excluding non-melanoma skin cancer) in females, accounting for approximately one in three cancers diagnosed among women.[1] In 2018, it is estimated that there will be over 266,000 incident cases of breast cancer.[2] Trends in breast cancer incidence have changed over time. From 1980 to 2003, an increase in breast cancer incidence was observed due to the introduction and widespread use of mammography screening as well as changes in breast cancer risk factors including reproductive patterns (e.g., delayed childbirth and having fewer children), obesity, and menopausal hormone use.[3] Despite a brief reduction in breast cancer incidence in the early 2000s,[4-6] breast cancer incidence has remained stable over the past decade.[7]

1-2. Breast cancer mortality

Breast cancer is the second leading cause of cancer death in the United States with almost 41,000 breast cancer deaths expected in 2018.[2] Over time, breast cancer mortality rates have decreased largely due to advances in effective screening (e.g., early detection with mammography) and treatment strategies (e.g., adjuvant chemotherapy and hormonal therapy in the 1980s and targeted therapies in the 1990s).[8,9] Overall, breast cancer mortality rates have decreased by 39% from 1990 to 2015.[3] As a result, an estimated 300,000 female breast cancer deaths in the United States have been averted through 2015, which has led to a growing population of breast cancer survivors.[3]

1-3. Breast cancer survivors

Currently, there are over 8 million women living with a history of a cancer diagnosis in the United States.[10] Among these women, breast cancer currently represents the largest group of survivors (44% of female survivors) due to the relatively high incidence and low mortality rates (Table 1-1).[10,11] Breast cancer survivors are also living longer after their diagnosis, which is giving rising to an increasing number of long-term survivors at risk for adverse effects from their initial breast cancer diagnosis and its related treatment.[11]

1-4. Definition of a breast cancer survivor

The National Coalition for Cancer Survivorship (NCCS) and the National Cancer Institute define a cancer survivor as an individual diagnosed with cancer from the time of diagnosis until the end of life.[12,13] Throughout this dissertation, "breast cancer survivor" will refer to a female with a breast cancer diagnosis regardless of time since diagnosis. Depending on our research question, we included women with *in situ* breast cancer in our definition of breast cancer survivor.

1-5. Established prognostic factors for breast cancer survival

Overall, 91% of women will survive 5 years or longer after a breast cancer diagnosis and 86% of women will survive 10 years or longer.[7] However, survival rates vary by pathological features of the tumor (e.g., stage and subtype), as well as clinical (e.g., treatment) and patient characteristics (e.g., age, race).

1-5a. Breast cancer stage

Breast cancer stage is an important prognostic factor that describes the extent of cancer at diagnosis and guides treatment options. In the United States, breast cancer stage is commonly

classified with either the TNM staging system or the summary stage system. This dissertation utilizes the TNM staging system, which is commonly used by clinicians, and incorporates information on tumor size (T), presence or absence of regional lymph node involvement (N), and presence or absence of distant metastasis (M).[7] TNM staging categorizes breast cancer into stage 0 for carcinoma *in situ* and stage I-IV for invasive breast cancer. Breast cancers up to stage III are considered early stage since cancer cells have not spread beyond the site of origin or axillary lymph nodes. Overall, breast cancer survival decreases with increasing stage. The five-year survival rate for women with localized disease is nearly 100% with 5-year survival rates decreasing for those with regional and distant stage disease to 85% and 27%, respectively.[14] Incident breast cancer cases are diagnosed primarily at the localized stage (62% of incident cases), therefore many women diagnosed with breast cancer will survive beyond five years after their diagnosis.[14]

1-5b. Breast cancer subtype

Breast cancer can be classified into several distinct molecular subtypes based on gene expression patterns (luminal A, luminal B, HER-2-enriched, and basal like).[15] These molecular subtypes are defined by the joint expression of three tumor markers at diagnosis: estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER-2). Approximately 70% of breast tumors are hormone receptor (HR)-positive (ER and/or PR-positive) and HER-2-negative (also known as Luminal A).[16] This subtype has been associated with the most favorable prognosis with 5-year breast cancer specific survival rates at 96%.[17,18] HR-positive tumors can also overexpress HER-2 (Luminal B subtype) and represent approximately 10% of breast cancer tumors.[16] In addition, approximately 5% of tumors are HR-negative and HER-2-positive (HER-2 overexpressing subtype).[16] HER-2-positive tumors are associated with slightly lower survival with 5-year breast cancer-specific survival estimates at

88% for HR-positive/HER-2-positive tumors and 81% for HR-negative/HER-2-positive tumors.[18] Finally, approximately 12% of breast tumors are classified as triple negative, which is defined as the absence of expression of ER, PR, and HER-2.[16] Triple negative tumors are often classified into the molecular subtype of basal-like. At diagnosis, these tumors are commonly associated with advanced stage,[19] higher grade,[20] and younger age.[21,22] Triple negative tumors also tend to occur more often in African-American women,[19-22] women with BRCA1 mutations[23] and women with a family history of cancer.[24] Prognosis among triple negative breast cancers tends to be poor, largely due to limited treatment options.[19]

1-5c. Breast cancer treatment

Advancements in treatment strategies over time have improved breast cancer survival rates. Treatment regimes, which are largely dependent on breast cancer stage and subtype, include surgery (e.g., breast conserving surgery [lumpectomy, partial mastectomy] or total mastectomy), radiation therapy, chemotherapy, hormone therapy, and targeted therapies.[25] Whether a patient receives systemic therapy (chemotherapy, hormone therapy, and targeted therapies) largely depends on the size of the tumor, lymph node involvement, and the presence of hormone receptors (ER/PR) and the HER-2 protein. Women with *in situ* cancer typically receive breast conserving surgery, but may also receive a combination of radiation and/or hormone therapy depending on their risk of recurrence or progression.[3] Women with early stage invasive cancer usually receive surgery plus a combination of radiation, chemotherapy, hormone and/or targeted therapies. Women with stage IV breast cancer will primarily receive systemic treatment.[3]

Radiation therapy is often used after surgery to eliminate any remaining cancer cells locally. External beam radiation therapy is considered the standard method with a typical course occurring 5 days per week for 5-7 weeks.[3] Overall, radiation has been shown to reduce local and

regional recurrence and breast cancer death rates.[26,27] Among women with breast conserving therapy, radiation has been shown to reduce the risk of recurrence by approximately 50% at 10 years and risk of breast cancer death by approximately 20% at 15 years.[28]

Chemotherapy is typically administered as a combination of drugs and these regimes are usually given for 3 to 6 months after surgery.[3] It is estimated that approximately 19% of women with stage I/II breast cancer and 82% of women with stage III breast cancer receive any chemotherapy.[7] Adjuvant chemotherapy significantly reduces the risk of recurrence and has been shown to reduce annual breast cancer death rates by approximately 38% among women aged ≤50 years at diagnosis and 20% among women aged 50-69 years at diagnosis.[29]

Hormone therapy is generally started after the completion of radiation and chemotherapy, if needed, for women with HR-positive tumors. The standard hormone therapy for premenopausal women is tamoxifen, a selective estrogen receptor modulator that interferes with estrogen binding to estrogen receptors, which is typically administered for at least 5-years. Adjuvant tamoxifen significantly reduces the risk of recurrence by approximately 40-50% in the first 10 years and reduces the risk of breast cancer death by approximately one-third in the first 15 years.[30] Postmenopausal women receive either aromatase inhibitors, which block the production of estrogen by preventing the conversion of androgens to estrogen, and/or tamoxifen for 5 to 10 years.[31] Overall, hormone therapy has also been shown to significantly reduce the risk of recurrence and breast cancer death in HR-positive tumors.[31] However, clinical trials are ongoing to determine the optimal timing and duration of hormone therapy.[3]

Tumors with HER-2 expression benefit from targeted therapies, which inhibit the growth of HER-2 proteins. Trastuzumab, a monoclonal antibody that targets the HER-2 protein, has become a standard part of treatment for HER-2 positive breast tumors.[3] When combined with

chemotherapy, trastuzumab has been shown to reduce recurrence risk by 52% and risk of breast cancer death by 33% for early-stage HER-2 positive breast tumors.[32]

1-5d. Age at diagnosis

Overall, the median age of breast cancer diagnosis is 62 years and the median age of breast cancer death is 68 years in the United States.[14] It is estimated that <2% of invasive breast cancer cases are diagnosed among women aged ≤35 years and most breast cancers occur among women aged ≥65 at diagnosis.[14,33] Previous studies have found that women diagnosed at a younger age tend to be diagnosed at a later stage[34,35] and with ER-negative tumors,[36,37] and subsequently have poorer overall survival compared to older women.[35,37-39] Menopausal status is also intrinsically tied to age and breast tumors that develop in premenopausal women tend to be associated with more aggressive tumor biology and more likely to be associated with BRCA1 mutations than postmenopausal breast cancer.[40,41] It is estimated that women aged <40 years at breast cancer diagnosis have a 5-year relative survival rate between 78-84% and women aged >60 years at diagnosis have a 5-year relative survival rate exceeding 90%.[36,41] The prognosis of older women also depends on the prevalence of comorbidities and reduced life expectancy, which can lead to potential over or under treatment and lower survival rates.[42-44]

1-5e. Race

Although breast cancer incidence is higher among white women, survival rates are lower among African-American women. In the United States, 5-year survival rates are approximately 91% among white women and 81% among African-American women.[14] Disparities in breast cancer survival are complex and may be due to several factors. Specifically, African-American women are more likely to be diagnosed at a younger age, and with poor prognostic factors (e.g., late

stage, hormone-receptor negative tumors).[45] In addition, differences in mammographic screening, access to treatment, comorbidities, and socioeconomic factors may play a role.[45] Although this dissertation does not explore factors by race, future studies are needed in more diverse populations.

1-6. Long-term mortality in breast cancer survivors

Epidemiologic studies have primarily examined long-term mortality in cohorts of breast cancer survivors only[46-54] with comparisons to the general population in a few studies.[55-59] Several studies have found that breast cancer survivors continue to have a higher risk of death from any cause even 10-20 years after diagnosis relative to the general population.[55-57] In addition, one prior study found that breast cancer survivors had an almost 4-fold higher risk of all-cause mortality, primarily due to breast cancer death, compared with the general population and survivors still had a 6-fold increased risk of breast cancer mortality even 25 years after diagnosis.[55] However, survivors diagnosed at older ages or with early stage disease may be more likely to die of conditions unrelated to their malignancy.[47,48,51] Only two prior studies have examined all-cause mortality in women with breast cancer relative to a cancer-free comparison from the same cohort[60,61] and none have examined this association by tumor characteristics, age at diagnosis, and temporal patterns. Therefore, it is difficult to determine if higher long-term mortality is driven by breast cancer and its related treatment or may also be in part due to increasing age, as well as menopausal status, lifestyle and other health factors.

1-7. Cardiovascular disease (CVD)

CVD is the leading cause of morbidity and mortality among women in the United States.[62] In the United States, it is estimated that approximately 1 in 3 women have CVD (~47.8 million women)

and 1 in 4 female deaths are due to CVD.[63,64] Risk factors for CVD can be broadly categorized as non-modifiable and modifiable. Non-modifiable risk factors include advancing age, African-American race, low socioeconomic status, and family history of CVD.[62] Modifiable risk factors include physical inactivity, smoking, poor diet (e.g., high in saturated fats), obesity, high cholesterol and other lipids, hypertension, and diabetes.[62]

1-7a. CVD in breast cancer survivors

For breast cancer survivors, CVD represents the leading cause of noncancer death.[51] Among breast cancer survivors aged ≥50 years, approximately 35% of non-breast cancer deaths are due to CVD.[51] Furthermore, women diagnosed at an early stage or at an older age, may be more likely to die from CVD than breast cancer.[52,53] Although several studies have reported an increased risk of CVD mortality in breast cancer survivors compared to the general population,[55,58,65] comparisons to cancer-free women within the same cohort are limited to two prior studies[60,61] and none have specifically evaluated whether CVD-mortality varies by tumor characteristics, age at diagnosis, and by long-term temporal patterns.

1-7b. Etiology of cardiovascular disease in breast cancer survivors

The etiology of CVD in breast cancer survivors is not well understood. It is hypothesized that an increased CVD risk may result from cardiotoxic effects of breast cancer treatment, which may begin to manifest at the time of treatment or as a late effect of treatment (Table 1-2).[63,66-69] Importantly, shared common risk factors may also contribute to CVD risk among breast cancer survivors.

Radiation therapy

There is a considerable amount of evidence supporting the role of radiation therapy on cardiovascular toxicity.[70] It is hypothesized that radiation, specifically to the left side of the chest wall, may increase CVD mortality by causing injury to the cardiac muscle. Yet some studies have shown no association between radiation and CVD mortality among women with left sided tumors compared to women with women with right-sided tumors.[71-73] It is also possible that current radiation therapy regimes, which are more targeted, are associated with a lower risk of cardiotoxic effects than older regimes.[72,74] Importantly, the effects of radiation therapy on CVD could occur as early as 5 years after therapy with some studies suggesting that risk may persist up to 30 years after treatment.[54,74,75] This underlies the importance of examining long-term mortality trends in breast cancer survivors.

Chemotherapy

Cardiovascular toxicity induced by chemotherapy has been well established.[70,76] Anthracyclines, which have been used to treat breast cancer since the 1970s, have been associated with adverse cardiovascular effects including left ventricular dysfunction and heart failure.[63,68] Older women and patients exposed to concomitant chemotherapy and radiation therapy are at the highest risk for cardiotoxic effects of anthracyclines.[63] Importantly, cardiotoxicity from anthracyclines can manifest either early or late after treatment. Alkylating agents (e.g., cisplatin and cyclophosphamides), taxanes, and antimetabolites have also been associated with adverse cardiovascular effects.[63] Chemotherapy may also indirectly impact CVD by inducing treatment-related menopause in premenopausal women.[77] Early menopause is associated with an increased risk of CVD due to lower levels of endogenous estrogen and subsequent unfavorable changes in lipid levels and hemostasis factors.[78-80]

Hormone therapy

Aromatase inhibitors, which deplete estrogen production, have been associated with a possible increased risk of CVD due to an increase in lipid and apolipoprotein concentrations.[76,81] Conversely, tamoxifen has been shown to exert beneficial effects on the cardiovascular system, which may be driven by lowering levels of total cholesterol, LDL cholesterol, apoprotein A1, and lipoprotein.[76] Despite these favorable effects on lipid profiles, large clinical trials have failed to show a protective effect of tamoxifen on cardiovascular endpoints.[63] Furthermore, some small studies have reported an increase in triglycerides among women treated with tamoxifen.[82,83]

HER-2 targeted therapies

Trastuzumab, a monoclonal antibody, has been associated with heart failure and left ventricular dysfunction, particularly when administered concomitantly or after anthracylcines.[69] Other targeted therapies, such as lapatinib, a small-molecule tyrosine kinase inhibitor approved for treatment of HER-2 metastatic cancer, may also be associated with a higher incidence of adverse cardiac events.[63]

Shared factors associated with breast cancer and CVD

There are several common factors between breast cancer and CVD incidence (Table 1-3).[63] These include increasing age, early menopause, hormone replacement therapy, smoking, obesity, and physical inactivity.[63,84-86] These shared factors underlie the importance for a cancer-free comparison within the same cohort to determine if breast cancer and its treatment have an independent effect on CVD burden in breast cancer survivors after accounting for these factors.

1-7c. CVD risk factors in breast cancer survivors

Breast cancer survivors have a higher prevalence of CVD risk factors, including hypercholesterolemia, hypertension, and diabetes, compared to cancer-free women.[87,88] However, whether CVD risk factors develop prior or after a breast cancer diagnosis remains unclear. A recent study found that adolescent and young adult breast cancer survivors had a higher incidence of diabetes and dyslipidemia, but not hypertension, compared to age-matched cancer-free women after adjusting for other risk factors including smoking, and overweight/obesity status.[88] CVD risk factors may develop in breast cancer survivors due to treatment related effects. However, CVD risk factors are also common among cancer-free women due to factors such as increasing BMI, physical inactivity, and an unhealthy diet.[64] No prior study has examined incident CVD risk factors in adult breast cancer survivors compared to cancer-free women within the same cohort.

1-8. Bone loss

Among women aged ≥50 years in the United States, it is estimated that approximately 15.4% have osteoporosis and 51.4% have low bone density.[89] Osteopenia and osteoporosis, both common conditions associated with varying degrees of bone loss, are initially diagnosed with measurements of bone mineral density (BMD) obtained from dual x-ray absorptiometry (DXA) scans. Although there are several methods to measure BMD, DXA scans are considered the gold standard. BMD is usually expressed in relative terms with a T-score calculated as a [(patient's BMD-young normal mean BMD)/ standard deviation of young normal mean BMD].[90] Based on WHO diagnostic criteria, osteopenia is defined as lower than average bone density with a T-score ranging from -1 to -2.5 (e.g., BMD levels are 1 to 2.5 standard deviations below the average level for young adults at peak bone mass).[90-92] Osteoporosis, characterized by even lower bone density, is defined as a T-score less than -2.5.[90-92] Among cancer-free women, loss in bone density is

primarily due to advancing age and menopause induced estrogen deficiency.[93,94] Modifiable factors also contribute to bone loss including low body weight, lack of physical activity, excess alcohol consumption, family history of bone fracture, cigarette smoking, low calcium intake, and vitamin D deficiency.[93,94] Untreated bone loss can lead to subsequent fractures, decreased quality of life, and death.[93] However, bone loss can be prevented with screening, lifestyle interventions (e.g., physical activity, smoking cessation, limiting alcohol intake, and adequate calcium and vitamin D intake), and therapy (e.g., bisphosphonates).[93]

1-8a. Bone loss in breast cancer survivors

Bone loss is highly prevalent among postmenopausal breast cancer survivors with up to 80% experiencing bone loss.[77] In addition, previous studies have shown that breast cancer survivors have a higher rate of fractures compared to cancer-free women.[95,96] For example, one study found that breast cancer survivors were almost 5-fold more likely to experience a vertebral fracture compared to the general population.[95] Few epidemiological studies have examined bone loss in breast cancer survivors compared to cancer-free women within the same cohort. Furthermore, these studies have been primarily conducted among older and long-term survivors and have not examined risk of bone loss by tumor subtypes and detailed treatment regimes.

1-8b. Etiology of bone loss in breast cancer survivors

The etiology of bone loss in cancer survivors may be due to both advancing age and menopause in addition to the effects of breast cancer treatment. Advancing age is associated with greater bone resorption and less bone formation, while menopause accelerates bone loss due to lower levels of endogenous estrogen.[97,98] Although the mechanisms underlying bone loss after menopause are not fully understood, it is well-established that estrogen plays a fundamental role

in maintaining bone density and estrogen deficiency is associated with a large increase in bone resorption.[99] Treatment related effects on bone loss have been commonly reported in survivors and breast cancer treatment can cause direct as well as indirect effects on bone health. Hormone therapies, such as tamoxifen and aromatase inhibitors, have been shown to increase the risk of bone loss in breast cancer survivors by subsquently reducing estrogen levels. Although tamoxifen may be protective against bone loss in postmenopausal women, it has been reported to increase bone loss in premenopausal women.[100,101] The underlying mechanisms of bone loss in breast cancer survivors may also be due to the direct toxic efects of chemotherapy on bone formation cells as well as treatment induced premature menopause.[102]

Outline of the dissertation

The chapters that follow will examine mortality, CVD risk factors, and bone loss in breast cancer survivors relative to cancer-free women. Chapter 2 examines the risk of long-term all-cause and CVD-related mortality among breast cancer survivors relative to cancer-free women in a population-based cohort study with over 20 years of follow-up. Chapter 3 evaluates the risk of developing CVD risk factors shortly after diagnosis in breast cancer survivors compared to cancer-free women in a cohort of women with familial risk for breast cancer. Chapter 4 examines the risk of bone loss in breast cancer survivors compared to cancer free women in a cohort of women with a family history of breast cancer. Chapter 5 concludes with a summary of our results, implications for breast cancer survivors, and future research directions.

Table 1-1. Estimated number of female cancer survivors by cancer site in the United States, 2016

Cancer site	N (%)
Breast	3,560,570 (44%)
Uterine	757,190 (9%)
Colon and rectum	727,350 (9%)
Thyroid	630,660 (8%)
Melanoma	612,790 (8%)
Non-Hodgkin lymphoma	324,890 (4%)
Lung and bronchus	288,210 (4%)
Uterine cervix	282,780 (3%)
Ovary	235,200 (3%)
Kidney	204,040 (3%)
All sites	8,156,120

Adapted from Miller et al. (2016)[10]
Source: Surveillance Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD

Table 1-2. Common breast cancer treatment and cardiovascular adverse effects

Cancer treatment	Cardiovascular adverse effects
Radiation therapy	Coronary artery disease, cardiomyopathy, valvular disease, pericardial disease, arrhythmia
Anthracyclines	Left ventricular dysfunction, heart failure, myocarditis, pericarditis, atrial fibrillation, ventricular tachycardia, ventricular fibrillation
Alkylating agents	Left ventricular dysfunction, heart failure, myocarditis, pericarditis, arterial thrombosis, bradycardia, atrial fibrillation, supraventricular tachycardia
Taxanes	Bradycardia, heart block, ventricular ectopy
Antimetabolites	Coronary thrombosis, coronary artery spasm, atrial fibrillation, ventricular tachycardia, ventricular fibrillation
Hormonal therapy	Venous thrombosis, thromboembolism, peripheral atherosclerosis, dysrhythmia, valvular dysfunction, pericarditis, heart failure
HER-2 directed therapies	Left ventricular dysfunction, heart failure

Adapted from Mehta et al. (2018)[63]

Table 1-3. Factors associated with developing breast cancer and cardiovascular disease

	Risk of breast cancer	Risk of cardiovascular disease
Increasing age	↑	↑
Healthy Diet[a]	↓	↓
Western Diet[b]	↑	↑
Light-moderate alcohol intake	↑	↓
Red/processed meat	↑	↑
Physical activity	↓	↓
Sedentary lifestyle	↑	↑
Premenopausal obesity	↓	↑
Postmenopausal obesity	↑	↑
Smoking	↑	↑
Early menarche	↑	↑
Early menopause	↓	↑
Hormone replacement therapy	↑	↑

Adapted from Mehta et al. (2018)[63]

↑ indicates an increased risk**;** ↓ indicates a decreased risk

[a] High in vegetables and fruits, poultry, fish, low-fat dairy products and whole grains

[b] High in red or processed meats, refined grains, sweets, and high-fat dairy products

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Chapter 2.

All-cause and cardiovascular disease mortality in breast cancer survivors: Results from a community-based cohort

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Abstract

Background: Long-term survival is common after breast cancer with overall 5-year survival rates now exceeding 90%. Understanding the risk of mortality in breast cancer survivors by tumor characteristics, age at diagnosis, and temporal patterns relative to cancer-free women will inform the effect of breast cancer and its related treatment on long-term survival and the need for increased medical surveillance and targeted interventions to reduce mortality.

Methods: We compared all-cause and cardiovascular disease (CVD)-related mortality in 628 women with early stage breast cancer and 3,140 age-matched cancer-free women in the CLUE II ("Give Us a Clue to Cancer and Heart Disease") cohort with over 20 years of follow-up. We calculated multivariable adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and CVD-related mortality using Cox proportional hazards regression. For CVD-related mortality, we also calculated sub-distribution HRs (sdHRs) using the Fine and Gray model to account for non-CVD death as a competing event. Models were stratified by tumor characteristics, age at diagnosis, and time since diagnosis.

Results: Over a median of 10.4 years of follow-up, 916 deaths were identified including 249 CVD-related deaths. The leading causes of death among breast cancer survivors were cancer (41%) followed by CVD (20%). Overall, in multivariable adjusted models, breast cancer survivors had a higher risk of dying compared to their cancer-free peers (HR=1.79, 95% CI=1.53-2.09) and this increased risk remained irrespective of stage and estrogen-receptor (ER)-status. Relative to cancer-free women, higher all-cause mortality persisted even 15 years after diagnosis among breast cancer survivors overall; however, breast cancer survivors diagnosed at age ≥70 years had a steady increase in all-cause mortality over time. An increased risk of CVD-related death was evident only after 8 years in breast cancer survivors compared to cancer-free women

(HR=1.71, 95% CI=1.03-2.83; sdHR=1.65, 95% CI=1.00-2.73), particularly among survivors with ER-positive tumors (HR=1.92, 95% CI=1.11-3.33; sdHR=1.85, 95% CI=1.06-3.20) and survivors aged ≥70 years at diagnosis (HR=2.43, 95% CI=1.40-4.21; sdHR=2.24, 95% CI=1.29-3.88).

Conclusion: Breast cancer survivors continue to have higher all-cause mortality due to their disease even 15 years after diagnosis; further research is needed to understand the persistent higher risk of all-cause mortality among all breast cancer survivors and the increasing risk over time among elderly breast cancer survivors. Early identification of CVD risk factors and interventions shortly after diagnosis may be warranted, particularly among elderly and ER-positive breast cancer survivors.

Introduction

In recent decades, advances in effective screening and treatment strategies have led to an increasing population of over 3.5 million breast cancer survivors in the United States.[1] With 5-year survival rates for breast cancer now exceeding 90%,[2] many women diagnosed with breast cancer will become long-term survivors at risk for disease progression, short- and long-term effects of treatment, and developing other co-morbidities. Therefore, it is of increasing importance to understand whether these women need increased medical surveillance and targeted interventions to reduce the risk of long-term mortality.

Previous studies on long-term mortality in breast cancer survivors have been primarily conducted among survivors only[3-12] with comparisons to the general population in a few studies.[13-17] Results from these studies suggest that excess all-cause mortality persists even 10-20 years after a breast cancer diagnosis, and is even higher among older survivors, relative to the general population.[13-17] Furthermore, many survivors are likely to die of conditions unrelated to their primary malignancies.[6,7] Notably, cardiovascular disease (CVD) is an issue of growing concern, particularly among women with favorable breast cancer phenotypes and among women diagnosed at an older age.[5-12] However, prior studies have been limited by either lacking individual level data on potential confounders or a cancer-free comparison; therefore it remains unclear whether all-cause and CVD-mortality may be due to breast cancer and its related treatment or whether the effects of aging, undergoing menopause, or lifestyle factors may also play a role.

Two recent studies have examined all-cause and CVD mortality in breast cancer survivors relative to cancer-free women within the same cohort.[18,19] Results from these studies suggest that

breast cancer survivors have a higher risk of dying from any cause even after accounting for age, menopause, and lifestyle factors.[18,19] In addition, one of these studies observed that risk of CVD may manifest only 7 years after diagnosis.[18] However, only one study examined the association by age at diagnosis and was restricted to post-menopausal survivors.[19] Furthermore, only one prior study had information on pre-diagnostic exposures[19] and only one examined temporal trends.[18] Both studies were limited by duration of follow-up and lacked detailed information on stage and breast cancer subtype.

To further understand long-term mortality in breast cancer survivors, we examined all-cause and CVD-related mortality in women diagnosed with breast cancer relative to age-matched cancer-free women in the community-based CLUE II ("Give use a Clue to Cancer and Heart Disease") cohort with over 20 years of follow-up. We also explored whether these associations differed by tumor characteristics (breast cancer stage and subtype), age at diagnosis, and time since diagnosis.

Methods

Study participants and design

The CLUE II ("Give use a Clue to Cancer and Heart Disease") cohort was formed in 1989 when 32,894 residents of Washington County, Maryland and the surrounding area completed an enrollment questionnaire and provided blood samples. Participants were subsequently followed with mailed questionnaires in 1996, 1998, 2000, 2003, and 2007. Updates on cancer incidence and mortality are conducted annually. The CLUE II study is approved by The Institutional Review Board of Johns Hopkins University.

For the present analysis, women aged 18 to ≤80 years with no history of cancer (except for non-melanoma skin cancer or cervical carcinoma *in situ*) at study enrollment were prospectively followed for breast cancer occurrence (N=14,420). All women diagnosed with a first primary breast cancer (stage I-III) through December 31st, 2015 were identified (n=628). Women diagnosed with stage 0, stage IV, or unknown breast cancer stage were excluded (n=161). A comparison group was then sampled from the same cohort. To ensure a similar distribution in age and follow-up time, five cancer-free women were randomly sampled without replacement and matched on age at diagnosis and time since enrollment to each woman diagnosed with breast cancer. The index date was the date of breast cancer diagnosis for women diagnosed with breast cancer. For comparison women (i.e., cancer-free women), the index date was the date of breast cancer diagnosis for their matched breast cancer survivor. Cancer-free women had to be alive and free of cancer at their index date.

Ascertainment of breast cancer

Our exposure of interest was a first primary stage I-III breast cancer diagnosis. In CLUE II, breast cancer diagnoses have been ascertained via linkage to the Washington County Cancer Registry and the Maryland Cancer Registry, as well as through medical record review and death certificates.[20] Information on tumor characteristics including date of diagnosis, age at diagnosis, stage, tumor size, and joint estrogen receptor (ER)/progesterone receptor (PR) status have been ascertained from cancer registries, medical record review, and pathology records. Initial treatment (none, surgery, chemotherapy, radiation and/or hormone therapy) was abstracted from medical records.

Ascertainment of death

Deaths were identified via death certificates, next of kin, obituaries, and the National Death Index through December 31, 2015. Death certificates were reviewed to identify the primary cause of death. We did not incorporate information on the contributing cause of death. Cause of death was coded using ICD-9 codes through 1998 and ICD-10 codes for all deaths after 1998. We considered deaths from any cause and deaths due to CVD. Deaths from CVD were identified if the following ICD codes were listed as the primary cause of death: 390-398, 402, 404, 410-429, I00-I09, I11, I13, and I20-I51. These codes were selected *a priori* to primarily represent deaths due to heart disease including ischemic heart disease, hypertensive heart disease, pulmonary heart disease, and other heart diseases (e.g., cardiomyopathy and heart failure). We did not include other CVD deaths due to essential hypertension, secondary hypertension, or cerebrovascular disease.

Ascertainment of covariates

Covariate information used in this analysis was from the interviewer-administered enrollment questionnaire in 1989. The questionnaire included information on date of birth, anthropometric factors (weight, height), lifestyle behaviors (smoking, alcohol use), reproductive/hormonal factors (oral contraceptive use, hormone use, and menopause status), medication use within the past 48 hours (e.g., medication for blood pressure, cholesterol, cardiovascular disease, and diabetes), and socio-demographic indicators (race/ethnicity, education). In addition, resting blood pressure and plasma total cholesterol was measured at the time of study enrollment.

Statistical analysis

Characteristics of breast cancer survivors and cancer-free women were compared with frequency distributions for categorical variables and means (SDs) for continuous variables. Breast cancer clinical and treatment characteristics were also summarized for breast cancer survivors.

Proportional mortality ratios

We calculated proportional mortality ratios (PMRs) among women with and without breast cancer to describe the contributions of specific causes of death (cancer, cardiovascular disease, other vascular disease including cerebrovascular and hypertensive disease, pulmonary disease, dementia, diabetes, infection, and other). PMRs were defined as the number of deaths due to a specific cause over the total number of deaths. PMRs were calculated overall and by tumor characteristics (stage, ER-status), age at diagnosis, and time since diagnosis.

All-cause mortality

We calculated Kaplan-Meier failure curves and used Cox proportional hazards regression to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause mortality in breast cancer survivors relative to cancer-free women. Time since index date was used as the underlying time metric. Women contributed person-time from the index date to the date of death or December 31st, 2015, whichever occurred first.

To account for multiple potential confounders, we used inverse probability weighting (IPW) to adjust for potential confounding in Kaplan Meier failure curves and regression models.[21-23] We used logistic regression models to construct the weights. Specifically, we fit a null model to calculate the marginal probability of being diagnosed with breast cancer (i.e., numerator of the weights) and then regressed breast cancer status on the potential confounders to obtain predicted

probabilities of breast cancer conditional on the potential confounders (i.e., denominator of the weight).[24] Robust standard errors were used to account for weights in the models. Potential confounders were identified *a priori* as variables that may be associated with both breast cancer incidence and mortality. These included menopausal status (premenopausal, postmenopausal), education (<12, 12, >12 years), smoking status (never, former, current), alcohol intake (0-3 drinks per month, ≥1 drinks per week), body mass index (BMI) (<25, 25-<30, ≥30kg/m^2) and oral hormone use (ever, never). Age was also included to account for any potential residual confounding. We assessed the proportional hazards assumption graphically with log-log survival plots and Schoenfeld residuals; there was no indication that the assumption of proportional hazards was violated.

We conducted several stratified analyses. First, we explored whether all-cause mortality varied among breast cancer survivors by tumor characteristics relative to cancer-free women. Specifically, we classified breast cancer survivors by stage (I, II, III) and ER-status (ER-positive, ER-negative). Second, to examine whether the association varied by time since index date, we stratified regression models by 0-5, >5-15 years, and >15 years since index date. These cut points were determined *a priori* and chosen based on clinically meaningful thresholds for risk of recurrence.[25] We then also restricted breast cancer survivors to those with the most favorable phenotypes (i.e., stage I or ER-positive tumors) and stratified the association by time. Finally, we stratified our models by age at index date (<70, ≥70 years) to determine whether the association varied by age. We chose the cut point of 70 years to be consistent with previous literature.[19] To test for significant differences across strata of time and age, we used multiplicative interaction terms between these factors and breast cancer status and the Wald test to determine statistical significance.

CVD-related mortality

To calculate risk of CVD-related mortality, we used a competing risk approach to account for non-CVD mortality as a competing event. Here, other causes of death (e.g., breast cancer) may preclude the event of interest (e.g., CVD-related mortality) and therefore remove women from the risk set before the event of interest is observed.[26] First, we used a non-parametric estimator of the cumulative incidence function to account for competing events.[27] Second, we estimated both the cause-specific hazard ratios (csHRs) and subdistribution hazard ratios (sdHRs).[26,28,29] csHRs for CVD-related mortality were estimated using Cox proportional hazards regression and non-CVD mortality was censored at the time of death. csHRs provided insight into whether breast cancer survivors had a higher instantaneous rate of CVD-related mortality but may not be interpreted as having a direct relationship to the probability of CVD-related mortality.[26] In this analysis, we interpret csHRs as the rate of CVD-related mortality in breast cancer survivors relative to cancer-free women among women who are still alive.[26,28] sdHRs for CVD-related mortality were estimated using Fine and Gray regression models, which account for the influence of non-CVD mortality as a competing event, and can be interpreted as having a direct relationship to the probability of CVD-related mortality.[26,28] Here we interpret sdHRs as the risk of CVD-related mortality in breast cancer survivors compared to cancer-free women.[28]

We accounted for multiple potential confounders and assessed the proportional hazards assumption with the same methods used for analyses examining all-cause mortality. Since the assumption of proportional hazards by breast cancer status was violated for CVD-related mortality, these models should be interpreted as the weighted average effect over the follow-up period.[26,30] In addition, we also report this association stratified by follow-up time.

We conducted the same series of stratified analyses as all-cause mortality. However, we stratified regression models by 0-8 vs. >8 years for CVD-related mortality to examine whether the

association varied by time. These cut points for CVD-related mortality were determined empirically based on the cumulative incidence curves. We did not include results for CVD-related mortality after 15 years in regression models due to small sample size.

Sensitivity analyses

We conducted a number of sensitivity analyses. First, we additionally adjusted for hypertension (yes, no), dyslipidemia (yes, no), diabetes medication (yes, no) and CVD medication (yes, no) in multivariable models. Second, we additionally adjusted multivariable models for race (white, black, other). Third, we adjusted for elapsed time from completion of the 1989 questionnaire to the index date to account for possible misclassification of covariates measured more distal to the index date. Fourth, we stratified our models by year of index date (<2000, ≥2000) to examine whether mortality trends may differ due to advances in breast cancer treatment over time. Fifth, we stratified regression models by an indicator for matched set to preserve the matching during follow-up. We did not use this as our primary approach since our analyses would have been limited by highly stratified data, particularly among subgroup analyses. Finally, since our comparison group could not develop an incident breast cancer during follow-up, we conducted a sensitivity analysis that treated breast cancer as a time-varying exposure to determine whether this may have biased our results. Specifically, in these analyses, women in the comparison group (i.e., unexposed) who were diagnosed with breast cancer after their index date were censored on their diagnosis date and at this time became members of the breast cancer group (i.e., exposed). We did not use this as our primary approach because the time of entry for women who were diagnosed with breast cancer after their index date (~3% of women in the comparison group) is not the date of diagnosis. This approach limits the ease of interpretability for our research question, which was focused on mortality after a breast cancer diagnosis and looking at trends over time since diagnosis. Furthermore, given that breast cancer is a rare occurrence and, in this

data, only 3% of the comparison group developed breast cancer, additional analytic approaches will likely be similar to our primary approach.

Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 14.0 (StataCorp LP, College Station, TX, USA). All statistical tests were two-side and P values ≤ 0.05 were considered statistically significant.

Results

Population characteristics

Table 2-1 describes characteristics of 3,768 women by breast cancer status (628 breast cancer survivors and 3,140 cancer-free women). As expected, the overall distributions of covariates were similar in breast cancer survivors compared to cancer-free women (mean age: 64.5 vs. 64.4 years; post-menopausal: 58.8 vs. 56.6%; mean BMI: 26.5 vs. 26.1 kg/m^2; never smokers: 61.8 vs. 61.1%). In addition, mean total cholesterol and blood pressure measurements and the proportion of heart disease and diabetes medications were similar among breast cancer survivors and cancer-free women at study enrollment. Among survivors, the median year of breast cancer diagnosis was 2002 (25^{th}-75^{th} percentile: 1996-2009) and women were more likely to be diagnosed at an early stage and with ER-positive tumors.

Leading causes of death

During 10.4 median years of follow-up, 34.6% of breast cancer survivors and 22.3% of cancer-free women died from any cause (Appendix 2-1; Appendix 2-2). Overall, cancer (41%) and CVD

(20%) were the leading causes of death in breast cancer survivors and CVD (29%) and cancer (17%) were the leading causes of death in women without breast cancer (Figure 2-1 A). Among women with stage I breast cancer, both cancer and CVD were the leading causes of death, and cancer was the leading cause of death among women with ER-positive tumors (Figure 2-1 B-C).

When we stratified PMRs by follow-up time, cancer remained the leading cause of death among breast cancer survivors and CVD remained the leading cause of death among cancer-free women throughout follow-up (Figure 2-2 A-C). The leading cause of death varied by time among women with stage I breast cancer (Figure 2-2 D-F) and cancer remained the leading cause of death over time in women with ER-positive tumors (Figure 2-2 G-I).

Among women aged <70 at index date, cancer was the leading cause of death for both women with and without cancer (Figure 2-3 A). However, among women aged ≥70 years at index date, CVD was the leading cause of death for both women with and without breast cancer (30% and 33%, respectively) (Figure 2-3 B). Cancer remained the leading cause of death throughout follow-up among women diagnosed at <70 years (Figure 2-3 C-E) and the leading cause of death varied by time among women diagnosed at ≥70 years (Figure 2-3 F-H).

All-cause mortality

Overall, death from any-cause was higher among breast cancer survivors relative to cancer-free women (HR=1.79, 95% CI=1.53-2.09) (Figure 2-4; additional numerical results are in Appendix 2-3). Stratification by cancer stage indicated that risk of all-cause mortality was greater with increasing stage when compared to cancer-free women (stage I: HR=1.53, 95% CI=1.25-1.86; stage II: HR=1.94; 95% CI=1.53-2.47; stage III: HR=4.86, 95% CI=3.12-7.56) (Figure 2-5 A). ER-positive and ER-negative survivors also had higher all-cause mortality compared to cancer-

free women (HR=1.81, 95% CI=1.52-2.14; HR=1.98, 95% CI=1.41-2.76, respectively) (Figure 2-5 B).

We then evaluated risk of all-cause mortality by time since diagnosis (Figure 2-4). Overall, death from any cause remained higher, even 15 years after diagnosis, in breast cancer survivors compared to cancer-free women (0-5 years: HR=1.91, 95% CI=1.45-2.52; >5-15 years, HR=1.70, 95% CI=1.37-2.11; >15 years, HR=1.84, 95% CI=1.28-2.66; p-interaction=0.91) (Figure 2-4). Survivors with stage I and ER-positive breast cancer also had an increased risk of all-cause mortality compared to cancer-free women even 15 years after diagnosis (Figure 2-5 A-B).

Next we examined all-cause mortality in breast cancer survivors compared to cancer-free women stratified by age at index date and then jointly stratified by age and time since index date (Table 2-2). Among women aged <70 years, risk of all-cause mortality was over two-fold higher among breast cancer survivors relative to cancer-free women (HR=2.20, 95% CI=1.72-2.80). Results were slightly attenuated among women aged ≥70 years (HR=1.71, 95% CI=1.42-2.06). Among women aged <70 years, risk of all-cause mortality was highest within the first 5 years after diagnosis in breast cancer survivors relative to cancer-free women (HR=3.52, 95% CI=2.19-5.63), however higher mortality persisted over time (>5-15 years, HR=1.78, 95% CI=1.24-2.56; >15 years, HR=2.05, 95% CI=1.28-3.29; p-interaction=0.28). Among women aged ≥70 years, risk of all-cause mortality significantly differed by time in breast cancer survivors compared to cancer-free women (p-interaction=0.05). Specifically, survivors had a 44% increased risk of all-cause mortality compared to cancer-free women within the first 5 years after diagnosis (HR=1.44, 95% CI=1.01-2.04) and an almost 3-fold higher risk of all-cause mortality after 15 years (HR=2.69, 95% CI=1.59-4.55).

CVD-related mortality

Overall, CVD-related mortality was higher among breast cancer survivors compared to cancer-free women; however, results were not statistically significant and further attenuated with competing risk regression (csHR=1.24, 95% CI=0.89-1.72; sdHR=1.09; 95% CI=0.78-1.51) (Figure 2-6; additional numerical results are in Appendix 2-3). The attenuation of the sdHR suggests that more breast cancer survivors had a competing event (i.e., non-CVD mortality such as breast cancer mortality) and therefore, breast cancer survivors are kept in the risk set in a greater proportion than those without breast cancer in competing risk regression.[26]

We observed no significant associations for CVD-related mortality among breast cancer survivors by stage relative to cancer-free women (Figure 2-7 A). However, women with ER-positive breast cancer had significantly higher CVD-related mortality compared to cancer-free women, yet results were slightly attenuated in competing risk regression (csHR=1.45, 95% CI=1.02-2.06; sdHR=1.28, 95% CI=0.90-1.82) (Figure 2-7 B). We observed no significant association with CVD-related mortality in ER-negative breast cancer survivors relative to cancer-free women (Figure 2-7 B). Results for the competing event, non-CVD mortality, stratified by tumor characteristics are shown in Appendix 2-4.

We then examined the risk of CVD-related mortality by time since diagnosis (Figure 2-6). Overall, risk of CVD-related death appeared to differ by time, although the difference was not statistically significant (p-interaction=0.14 and 0.13 for csHRs and sdHRs, respectively). Within the first 8 years after diagnosis, there was no difference in CVD-related mortality among breast cancer survivors compared to cancer-free women (csHR=0.99, 95% CI=0.59-1.66; sdHR=0.94, 95% CI=0.56-1.58). After 8 years, risk of CVD-related mortality was significantly higher among breast cancer survivors relative to cancer-free women (csHR=1.71, 95% CI=1.03-2.83;

sdHR=1.65, 95% CI=1.00-2.73). Results for non-CVD mortality stratified by time are shown in Appendix 2-5.

CVD-related mortality did not appear to differ by time in stage I breast cancer survivors relative to cancer-free women (p-interaction=0.42 for csHRs; p-interaction=0.45 for sdHRs) (Figure 2-7 A). However, an increased risk of CVD-related mortality may begin to manifest 8 years after diagnosis in women with ER-positive breast cancer relative to cancer-free women (0-8 years: csHR=1.10, 95% CI=0.62-1.93, sdHR=1.06, 95% CI=0.60-1.86; >8 years: csHR=1.92, 95% CI=1.11-3.33, sdHR=1.85, 95% CI=1.06-3.20; p-interaction=0.17 for csHRs and sdHRs) (Figure 2-7 B). Results for non-CVD mortality in stage I and ER-positive survivors stratified by time are shown in Appendix 2-5.

Finally, we evaluated CVD-related mortality in breast cancer survivors compared to cancer-free women stratified by age at index date (Table 2-3). We observed no significant association between breast cancer status and CVD-related mortality among women aged <70 years at index date (csHR=0.77, 95% CI=0.35-1.70; sdHR=0.68, 95% CI=0.31-1.49). Among women aged ≥70 years, breast cancer survivors had significantly higher CVD-related mortality compared to cancer-free women, although results were attenuated in competing risk regression (csHR=1.58, 95% CI=1.10-2.27; sdHR=1.25, 95% CI=0.87-1.80).

In Table 2-3, we further stratified the association jointly by both age and then time, and observed no significant temporal trends among women aged <70 years. Among women aged ≥70 years, CVD-related mortality appeared to differ by time among breast cancer survivors compared to cancer-free women (p-interaction=0.06 for csHRs; p-interaction=0.07 for sdHRs). Specifically, we observed no significant association within the first 8-years in breast cancer survivors relative to cancer-free women (csHR=1.16, 95% CI=0.67-1.99; sdHR=1.10, 95% CI=0.64-1.88) and an

over two-fold higher risk of CVD-related mortality after 8 years (csHR=2.43, 95% CI=1.40-4.21; sdHR=2.24, 95% CI=1.29-3.88). Results for non-CVD mortality stratified by age and jointly by age and time are shown in Appendix 2-6.

Sensitivity analyses

First, results were similar to our primary analyses when we additionally adjusted for hypertension, high cholesterol, diabetes medication and CVD medication in multivariable models (Appendix 2-3). Second, results were also similar when we adjusted for race or elapsed time from completion of the 1989 questionnaire to the index date (data not shown). Third, analyses that stratified by year of index date (<2000, ≥2000) did not significantly differ for all-cause or CVD-related mortality (data not shown). Fourth, regression models that stratified by an indicator for matched set were similar compared to the primary analyses (Appendix 2-7). Finally, in sensitivity analyses using a breast cancer diagnosis as a time-varying exposure, 3% of cancer-free women developed breast cancer after their index date and thus were censored on their diagnosis date and became exposed at that time. Given the small proportion of women who developed breast cancer after their index date, overall results in this sensitivity analysis were similar to our primary analyses (Appendix 2-7).

Discussion

Overall, this study demonstrated that breast cancer survivors had a 79% higher risk of all-cause mortality relative to cancer-free women and an increased risk persisted irrespective of stage and ER-status for up to 15 years. All-cause mortality was similar by age at diagnosis; however trends in all-cause mortality differed by time among younger and older survivors. Women aged <70

years at diagnosis had the highest risk of dying within the first 5 years compared to cancer-free women of similar age. In contrast, women aged ≥70 years at diagnosis had a steady increase in all-cause mortality over time with a 44% increased risk of all-cause mortality within 5 years of diagnosis and an almost 3-fold increased risk of all-cause mortality after 15 years. We further found that risk of CVD-related mortality may be higher among breast cancer survivors, particularly among those diagnosed at an older age or with ER-positive tumors, relative to cancer-free women. However, a higher risk of CVD-related mortality only begins to manifest after 8 years post-diagnosis.

To date, only two studies have examined all-cause and CVD-mortality in breast cancer survivors relative to cancer-free women within the same cohort.[18,19] Our overall finding that risk of all-cause mortality was higher in breast cancer survivors compared to cancer-free women is consistent with these studies.[18,19] The first of these studies, conducted by Bradshaw and colleagues in the Long Island Breast Cancer Study Project with up to 13.5 years of follow-up, found that breast cancer survivors had an 80% increased risk of all-cause mortality compared to cancer-free women (HR=1.8, 95% CI=1.5-2.1) even after accounting for age, menopause and other potential confounding factors.[18] The second study, conducted by Park and colleagues among post-menopausal women in the Women's Health Initiative, reported a higher total mortality rate in women with localized breast cancer compared to cancer-free women after 10 years of follow-up.[19] However, these studies did not examine all-cause mortality by breast cancer characteristics and were limited by duration of follow-up. Adding to this literature, we also observed an increased risk of all-cause mortality irrespective of stage and ER status and even 15 years after diagnosis among all breast cancer survivors and even among survivors with stage I or ER-positive tumors.

To our knowledge, this is the first prospective study to examine all-cause mortality stratified jointly by age at diagnosis and time since diagnosis in breast cancer survivors compared to cancer free women within the same cohort. Although Park and colleagues reported a 20% increased risk of all-cause mortality in older breast cancer survivors, aged 70-79 years at diagnosis, compared to cancer-free women of similar age (HR=1.20, 95% CI=1.04-1.39), this study did not examine all-cause mortality among women aged <70 years or by temporal trends. The underlying mechanisms of higher all-cause mortality in older breast cancer survivors may be related to an increased risk for adverse cardiac outcomes due to treatment related cardiotoxicity[31] or conversely under-treatment due to lowered functional status, higher prevalence of comorbidities, and low life expectancy.[32-35] Therefore, the risks and benefits of treatment need to be carefully balanced among older women diagnosed with breast cancer and deserves further study.

Our finding that breast cancer survivors overall may have a higher risk of CVD-related mortality relative to a comparable group of cancer-free women after 8 years is similar to the previously mentioned study by Bradshaw and colleagues conducted among the Long Island Breast Cancer Study Project.[18] This study observed that CVD mortality increased around 7 years post-diagnosis among breast cancer survivors relative to cancer-free women (0-7 years: csHR=0.80, 95% CI=0.53-1.2, sdHR=0.59, 95% CI=0.40-0.87; 7+ years: csHR=1.8, 95% CI=1.3-2.5, sdHR=1.9, 95% CI=1.4-2.7; p-interaction=0.001). Our study adds to this literature by demonstrating that risk of CVD-related mortality may be higher among older women and women diagnosed with ER-positive breast cancer relative to cancer-free women; yet this risk only becomes apparent 8 years after diagnosis. However, our results did not significantly differ by time and therefore must be interpreted with caution. Additional larger studies are needed to confirm these results.

Although CVD mortality has also been commonly reported in studies among breast cancer survivors,[5-11] the etiology of CVD mortality among breast cancer survivors is not well

understood. Several underlying mechanisms have been proposed, including a higher prevalence of CVD risk factors (e.g. older age, obesity, hypertension, diabetes, and physical inactivity) among breast cancer survivors[36] and cardiotoxic effects from breast cancer treatment (e.g., radiation, chemotherapy, hormone therapies, and targeted therapies).[37] Adding to the literature, our findings may have particularly important clinical implications for women diagnosed at an older age or with ER-positive tumors and speak to the importance of potentially implementing interventions shortly after diagnosis to reduce risk of CVD death (e.g., monitoring of blood pressure, lipid profiles, and weight). This underlies the need for future studies to examine both short- and long-term CVD-risk factors and other comorbidities, as well as the effects of treatment among these groups.

Strengths of our study include a cancer-free comparison group and the ability to match the comparison group on age and time to breast cancer survivors from the same community-based cohort. With a cancer-free comparison group, we were able to identify differences in mortality between these groups after adjusting for potential confounding factors as well as examine patterns of risk (e.g., whether risk differs by time, age or other prognostic factors). Furthermore, follow-up time ranged up to 25.9 years and therefore we were able to examine associations between breast cancer status and long-term mortality over a long duration of follow-up.

There are several limitations of our study. First, potential confounders were assessed at enrollment into the CLUE II cohort in 1989 and the mean time from 1989 to index date was 13.3 years (SD=7.3 years). However, our results did not change when we adjusted for elapsed time from 1989 to the index date to account for potential misclassification of covariates measured more distal to the index date. Furthermore, we lacked information on cardiovascular disease and complete information on cardiovascular risk factors. However, our results were similar when we additionally adjusted for hypertension, hyperlipidemia, and medication use. In addition, we did

not have complete information on treatment and therefore were unable to conduct subgroup analyses by breast cancer treatment; further studies are needed to examine the effects of treatment in breast cancer survivors relative to a cancer-free comparison. Second, it is possible that excluding women who developed breast cancer from our reference group may have biased our results. However we treated our exposure, breast cancer diagnosis, as a time-varying non-reversible exposure in a sensitivity analysis and only a small proportion (3%) of women in the comparison cohort developed breast cancer after their index date. Overall results were similar to our primary analysis in this sensitivity analysis. Third, the underlying cause of death was ascertained through death certificates and it is possible that cause of death was misclassified. Previous studies have shown that deaths due to heart disease may be overestimated[38] and the accuracy of cancer deaths may vary by cancer site.[39] Although the magnitude of misclassification for breast cancer has been shown to be minimal,[40,41] we cannot rule out the possibility of misclassification in our outcome. Finally, our study consisted of primarily white participants (>98%) and results may not be generalizable to women of other racial groups. Future studies are needed to examine these associations over time among more diverse populations.

In conclusion, our results show that breast cancer survivors, irrespective of stage and ER-status, continue to have higher all-cause mortality due to their disease, compared to their cancer-free peers. Further research is needed to understand persistent higher all-cause mortality in breast cancer survivors and increased risk over time among elderly breast cancer survivors. Elderly and ER-positive breast cancer survivors may also have a higher risk of dying from CVD than cancer-free women and therefore primary and secondary prevention of CVD may be warranted. Future larger prospective cohort studies are needed to confirm these findings.

Table 2-1. Participant characteristics in breast cancer survivors and cancer-free women in the CLUE II cohort study

Characteristic	Cancer-free women (N=3,140)	Survivors (N=628)
Age at index date, mean years (SD)	64.4 (11.8)	64.5 (11.8)
Time from enrollment to index date, mean years (SD)	13.3 (7.3)	13.3 (7.3)
White, %	98.4	99.0
Education, %		
<12 years	20.8	18.8
12 years	48.5	46.2
>12 years	30.7	35.0
Postmenopausal, %	56.6	58.8
Body Mass Index, mean kg/m^2 (SD)	26.1 (5.1)	26.5 (5.4)
Body Mass Index, kg/m^2, %		
<25	48.8	45.1
25-<30	30.4	32.5
≥30	20.7	22.5
Missing	0.1	0.0
Smoking status, %		
Never	61.1	61.8
Former	21.4	23.7
Current	17.5	14.5
Alcohol intake, %		
Never or <1 drink per month	51.4	51.4
1-3 drinks per month	12.2	13.1
≥1 drinks per week	32.7	32.2
Missing	3.7	3.3
Oral contraceptive use, %		
Never	60.8	63.1
Former	31.8	29.1
Current	6.2	6.7
Missing	1.1	1.1
Hormone use, %		
Never	80.1	80.1
Former	4.2	3.8
Current estrogen only	9.1	7.8
Current estrogen + progesterone or progesterone only	3.2	4.1
Missing	3.4	4.1
Systolic blood pressure, mean mmHg (SD)	125.9 (35.6)	126.3 (38.6)
Diastolic blood pressure, mean mmHg (SD)	79.2 (34.1)	79.9 (37.9)
Plasma total cholesterol, mean mg/dL (SD)	228.0 (119.3)	223.5 (96.8)
Current high blood pressure medication use, %	19.2	18.6
Current high cholesterol medication use, %	4.4	3.8
Current CVD medication use, %	25.0	24.0
Current diabetes medication use, %	2.1	2.2
Year of breast cancer diagnosis, median (25th-75th percentile)	--	2002 (1996-2009)
Breast cancer stage, %		
I	--	59.7
II	--	31.4
III	--	7.5
Unknown/Missing	--	1.4
Tumor size (cm), %		
≤2	--	69.1
>2	--	23.4
Missing	--	7.3

Estrogen receptor status, %		
Positive	--	73.7
Negative	--	16.7
Missing	--	9.6

Abbreviations: CVD, cardiovascular disease

Table 2-2. Hazard ratios and 95% confidence intervals for all-cause mortality according to breast cancer status stratified by age at diagnosis and the joint association of age at diagnosis and time since diagnosis

	Deaths/person-years	HR (95% CI)[a]	p-value[b]
Age at diagnosis			
Age <70 years			
Cancer-free women	242/25,740	1.00 (ref)	
Breast cancer survivors	92/4,611	2.20 (1.72-2.80)	0.10
Age ≥70 years			
Cancer-free women	457/9,597	1.00 (ref)	
Breast cancer survivors	125/1,660	1.71 (1.42-2.06)	
Time and age			
Age <70 years			
0-5 years			
Cancer-free women	44/9,251	1.00 (ref)	
Breast cancer survivors	29/1,793	3.52 (2.19-5.63)	
>5-15 years			0.28
Cancer-free women	125/12,434	1.00 (ref)	
Breast cancer survivors	40/2,208	1.78 (1.24-2.56)	
>15 years			
Cancer-free women	73/3,985	1.00 (ref)	
Breast cancer survivors	23/662	2.05 (1.28-3.29)	
Age ≥70 years			
0-5 years			
Cancer-free women	147/4,648	1.00 (ref)	
Breast cancer survivors	41/901	1.44 (1.01-2.04)	
>5-15 years			0.05
Cancer-free women	246/4,292	1.00 (ref)	
Breast cancer survivors	70/717	1.76 (1.35-2.30)	
>15 years			
Cancer-free women	64/635	1.00 (ref)	
Breast cancer survivors	14/54	2.69 (1.59-4.55)	

Abbreviations: HR, hazard ratio; CI, confidence interval

[a] Adjusted for age (years), menopausal status (premenopausal, postmenopausal), education (<12, 12, >12 years), smoking status (never, former, current), alcohol intake (0-3 drinks/month, ≥1 drinks/week), body mass index (<25, 25-<30, ≥30 kg/m^2), oral hormone use (ever, never) using inverse probability weighting

[b] P-interaction for the cross-product term of breast cancer status and listed categories

Table 2-3. Hazard ratios and 95% confidence intervals for cardiovascular disease-related mortality according to breast cancer status stratified by age at diagnosis and the joint association of age at diagnosis and time since diagnosis

	Deaths/person-years	csHR (95% CI)[a]	p-value[b]	sdHR (95% CI)[a]	p-value[b]
Age at diagnosis					
Age <70 years					
Cancer-free women	56/25,740	1.00 (ref)		1.00 (ref)	
Breast cancer survivors	7/4,611	0.77 (0.35-1.70)	0.11	0.68 (0.31-1.49)	0.18
Age ≥70 years					
Cancer-free women	149/9,597	1.00 (ref)		1.00 (ref)	
Breast cancer survivors	37/1,660	1.58 (1.10-2.27)		1.25 (0.87-1.80)	
Time and age					
Age <70 years					
0-8 years					
Cancer-free women	19/13,821	1.00 (ref)		1.00 (ref)	
Breast cancer survivors	1/2,627	0.35 (0.05-2.60)	0.75	0.34 (0.05-2.51)	0.74
>8 years					
Cancer-free women	20/7,864	1.00 (ref)		1.00 (ref)	
Breast cancer survivors	2/1,374	0.53 (0.12-2.26)		0.51 (0.12-2.19)	
Age ≥70 years					
0-8 years					
Cancer-free women	73/6,577	1.00 (ref)		1.00 (ref)	
Breast cancer survivors	16/1,248	1.16 (0.67-1.99)	0.06	1.10 (0.64-1.88)	0.07
>8 years					
Cancer-free women	48/2,364	1.00 (ref)		1.00 (ref)	
Breast cancer survivors	18/370	2.43 (1.40-4.21)		2.24 (1.29-3.88)	

Abbreviations: csHR, cause-specific hazard ratio; sdHR, subdistribution hazard ratio; CI, confidence interval

[a] Adjusted for age (years), menopausal status (premenopausal, postmenopausal), education (<12, 12, >12 years), smoking status (never, former, current), alcohol intake (0-3 drinks/month, 1+ drinks/week), body mass index (<25, 25-<30, ≥30 kg/m^2), oral hormone use (ever, never) using inverse probability weighting

[b] P-interaction for the cross-product term of breast cancer status and listed categories

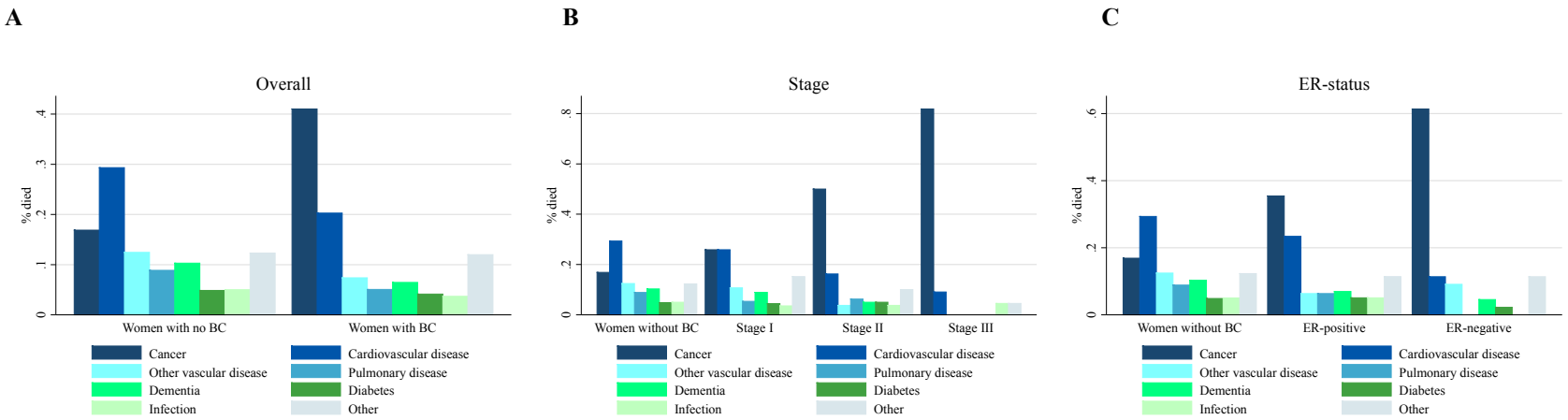


Figure 2-1. Proportional mortality ratios in cancer-free women and breast cancer survivors (a) overall and stratified by (b) stage and (c) estrogen-receptor (ER) status

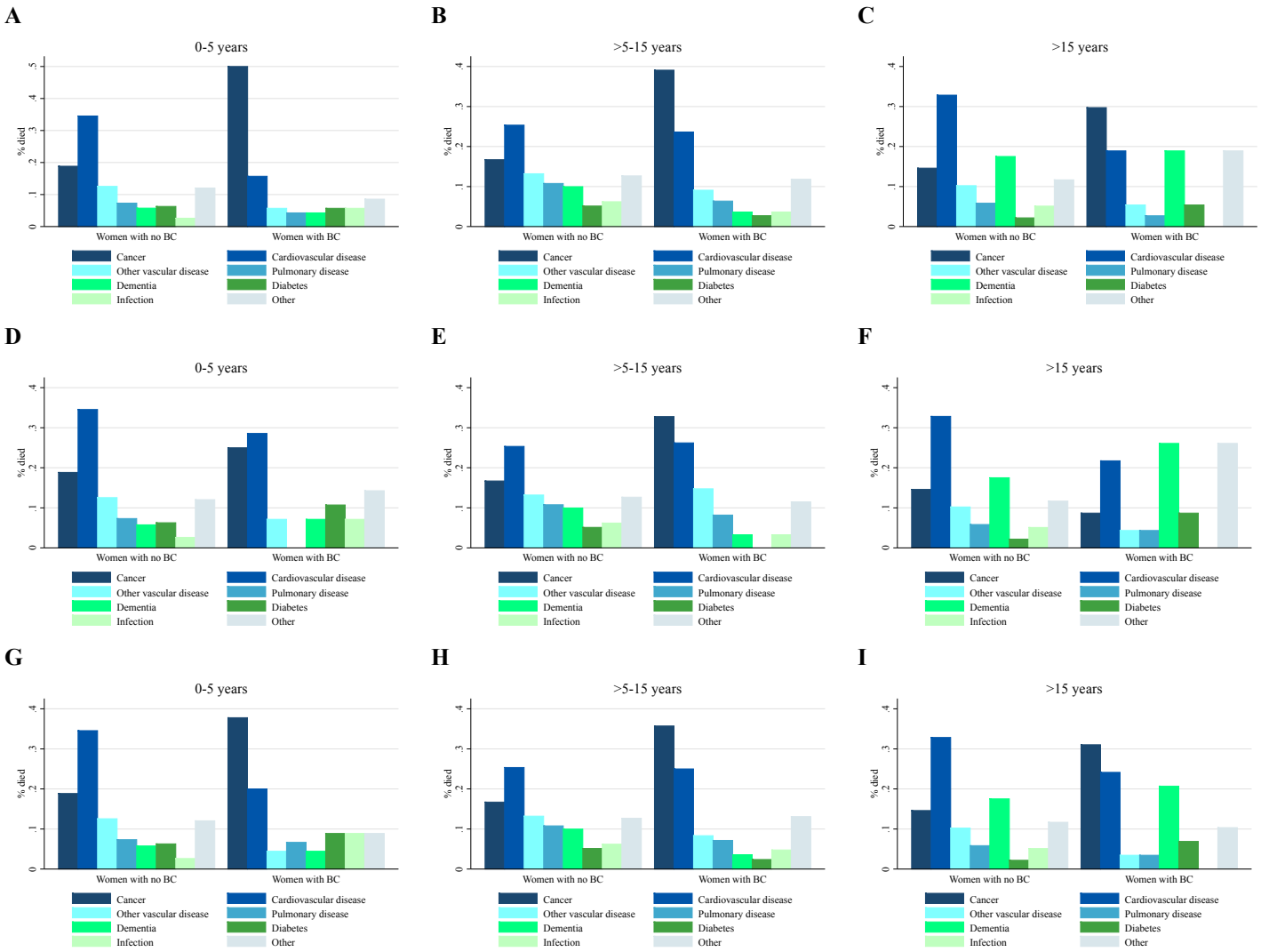


Figure 2-2. Proportional mortality ratios in cancer-free women and breast cancer survivors (a-c) overall and restricted to (d-f) stage I tumors and (g-i) estrogen-receptor positive tumors, stratified by time since diagnosis

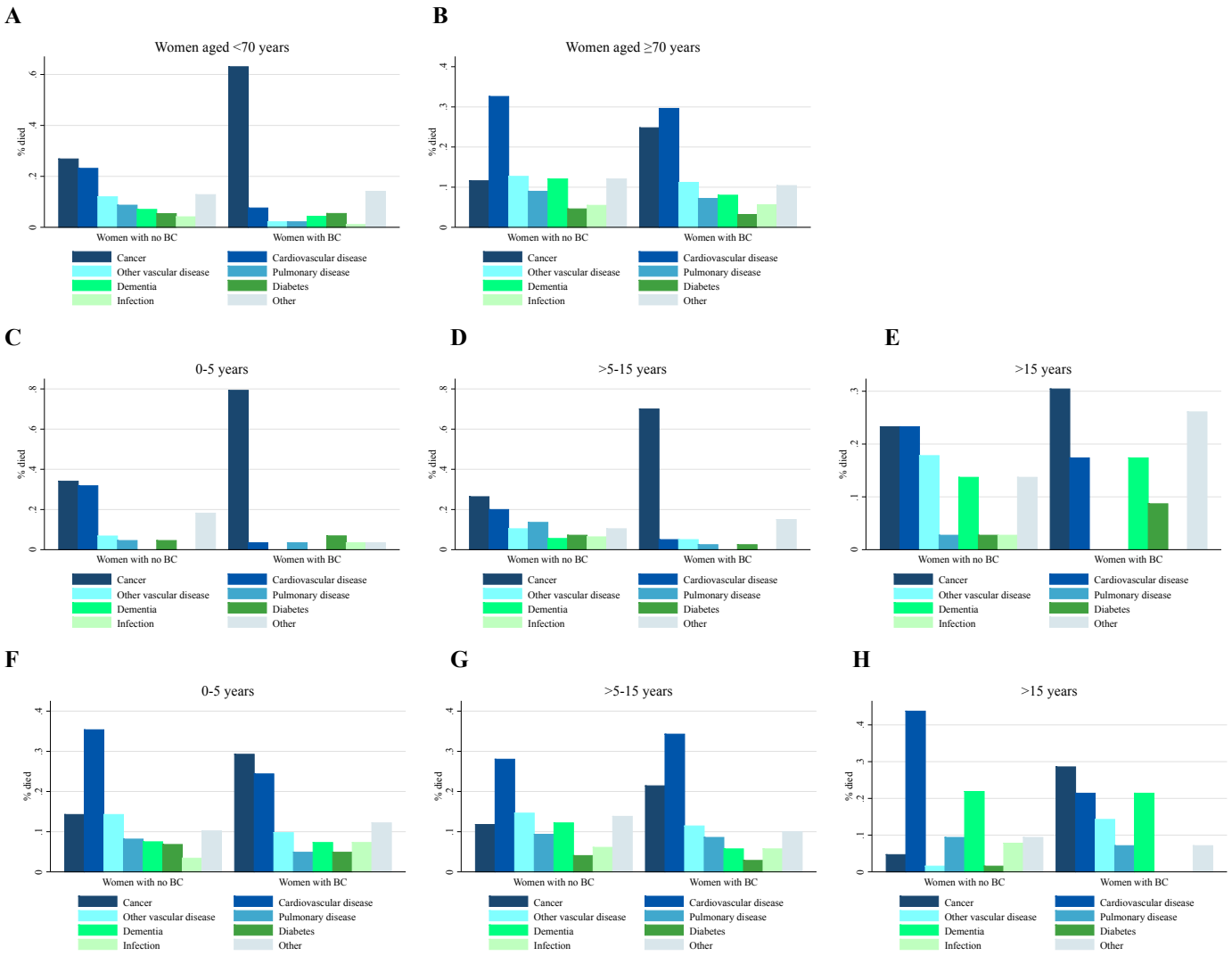
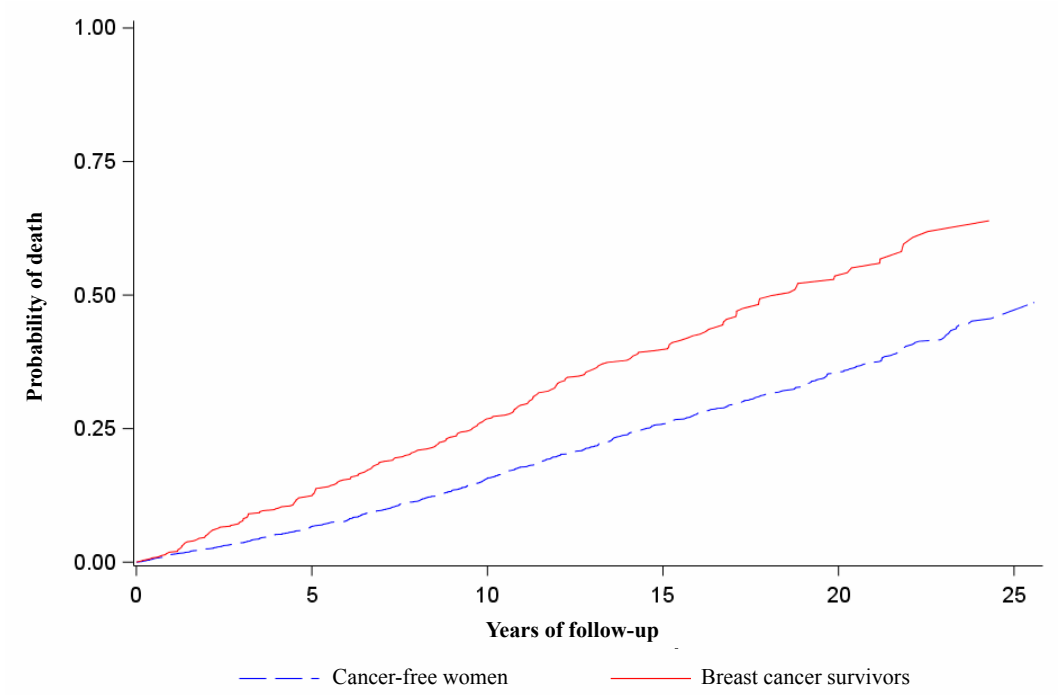


Figure 2-3. Proportional mortality ratios according to breast cancer status stratified by (a-b) age at diagnosis and by time since diagnosis in (c-e) women aged <70 years and (f-h) women aged ≥70 years

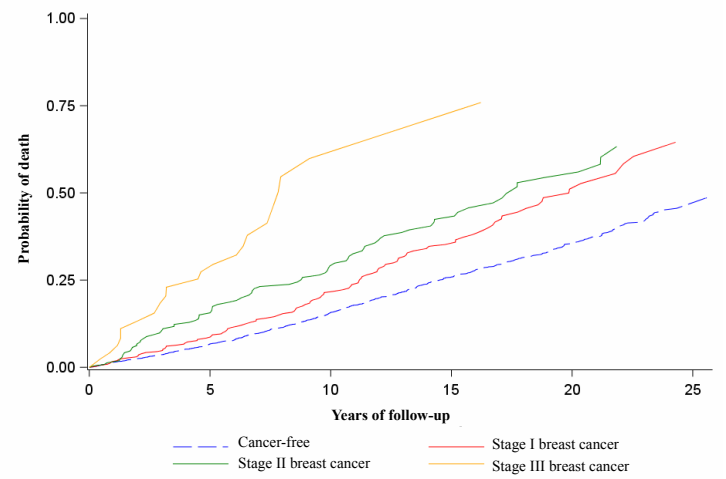


	Cancer-free	Survivors	
	Events/PT	Events/PT	HR (95% CI)
Overall	699/35246	217/6335	1.79 (1.53-2.09)
Time since diagnosis			
0-5 years	191/13900	70/2694	1.91 (1.45-2.52)
>5-15 years	371/16726	110/2924	1.70 (1.37-2.11)
>15 years	137/4620	37/716	1.84 (1.28-2.66)
p-interaction			0.91

Figure 2-4. Adjusted Kaplan-Meier failure curves and hazard ratios (95% confidence intervals) for all-cause mortality in breast cancer survivors compared with cancer-free women. Hazard ratios (95% confidence intervals) are presented overall and stratified by time since diagnosis in breast cancer survivors compared with cancer-free women[a,b]

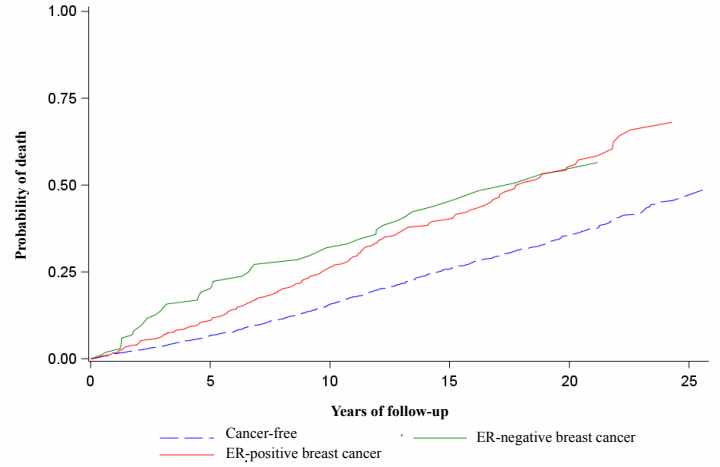
Abbreviations: PT, person-years; HR, hazard ratio; CI, confidence interval; IPW, inverse probability weighting
[a] Adjusted for age, menopausal status, education, smoking status, alcohol intake, body mass index, and oral hormone use using IPW
[b] The reference group is cancer-free women for all HRs (95% CIs)

A



	Cancer-free Events/PT	Survivors Events/PT	HR (95% CI)
Overall			
Stage I	699/35246	112/3803	1.53 (1.25-1.86)
Stage II	699/35246	81/2121	1.94 (1.53-2.47)
Stage III	699/35246	22/283	4.86 (3.12-7.56)
Time since diagnosis among stage I			
0-5 years	191/13900	28/1615	1.28 (0.86-1.90)
>5-15 years	371/16727	61/1766	1.55 (1.18-2.04)
>15 years	137/4620	23/418	1.93 (1.24-3.00)
p-interaction			0.17

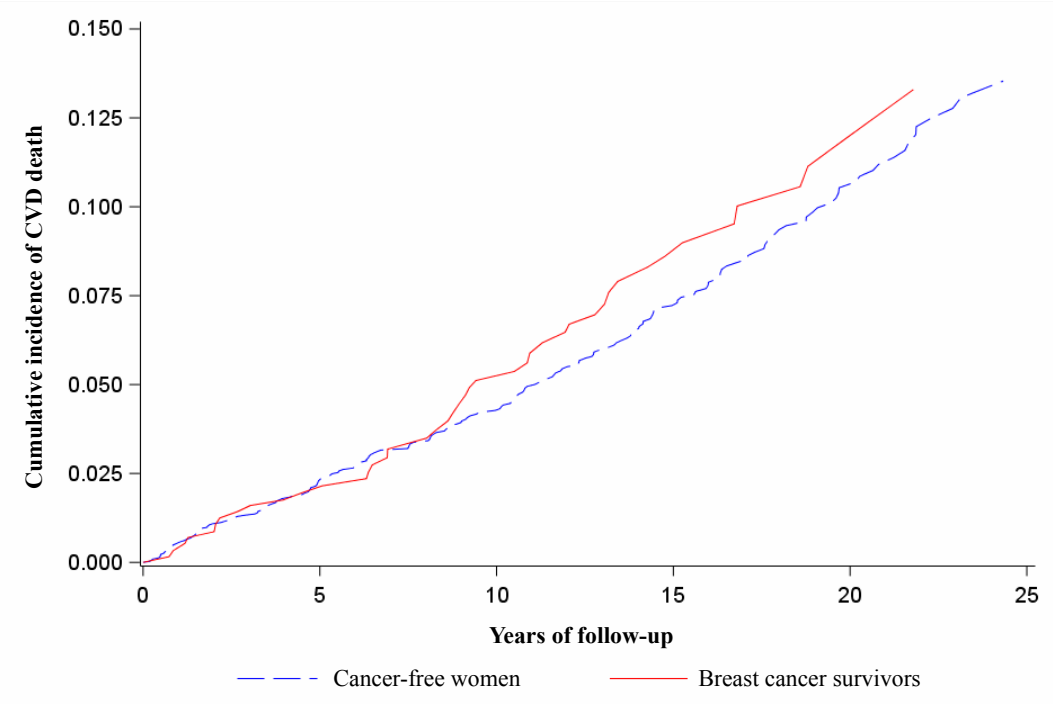
B



	Cancer-free Events/PT	Survivors Events/PT	HR (95% CI)
Overall			
ER-positive	699/35246	158/4614	1.81 (1.52-2.14)
ER-negative	699/35246	44/1128	1.98 (1.41-2.76)
Time since diagnosis among ER-positive			
0-5 years	191/13,900	45/1993	1.66 (1.20-2.31)
>5-15 years	371/16727	84/2114	1.81 (1.42-2.30)
>15 years	137/4620	29/507	2.11 (1.42-3.14)
p-interaction			0.36

Figure 2-5. Adjusted Kaplan-Meier failure curves and hazard ratios (95% confidence intervals) for all-cause mortality in breast cancer survivors stratified by (a) cancer stage and (b) estrogen-receptor status, compared with cancer-free women. Hazard ratios (95% confidence intervals) are presented overall and stratified by time since diagnosis in (a) survivors restricted to stage I cancer and (b) survivors restricted to estrogen-receptor positive tumors, compared with cancer-free women[a,b]

Abbreviations: PT, person-years; HR, hazard ratio; CI, confidence interval; IPW, inverse probability weighting
[a] Adjusted for age, menopausal status, education, smoking, alcohol use, body mass index, oral hormone use using IPW
[b] The reference group is cancer-free women for all HRs (95% CIs)



	Cancer-free	Survivors		
	Events/PT	Events/PT	csHR (95% CI)	sdHR (95% CI)
Overall	205/35246	44/6335	1.24 (0.89-1.72)	1.09 (0.78-1.51)
Time since diagnosis				
0-8 years	92/20398	17/3875	0.99 (0.59-1.66)	0.94 (0.56-1.58)
>8 years	68/10228	20/1744	1.71 (1.03-2.83)	1.65 (1.00-2.73)
p-interaction			0.14	0.13

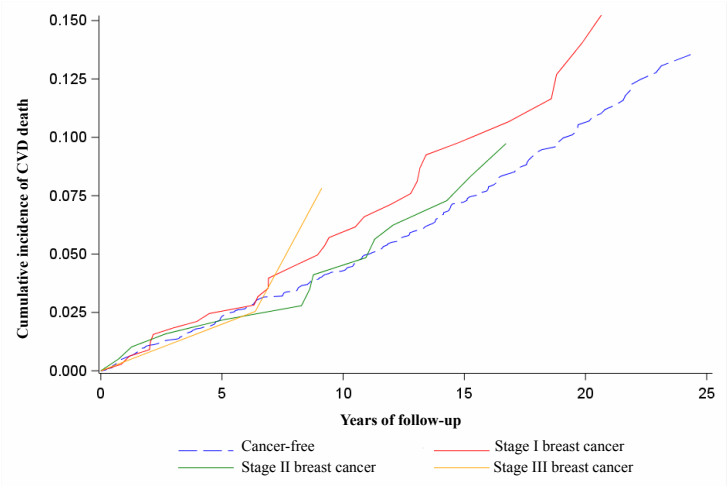
Figure 2-6. Adjusted cumulative incidence function and hazard ratios (95% confidence intervals) for cardiovascular–related mortality in breast cancer survivors compared with cancer-free women. Hazard ratios (95% confidence intervals) are presented overall and stratified by time since diagnosis in breast cancer survivors compared with cancer-free women[a,b]

Abbreviations: PT, person-years; csHR, cause-specific hazard ratio; sdHR, subdistribution hazard ratio; CI, confidence interval; IPW, inverse probability weighting

[a] Adjusted for age, menopausal status, education, smoking status, alcohol intake, body mass index, oral hormone use using IPW

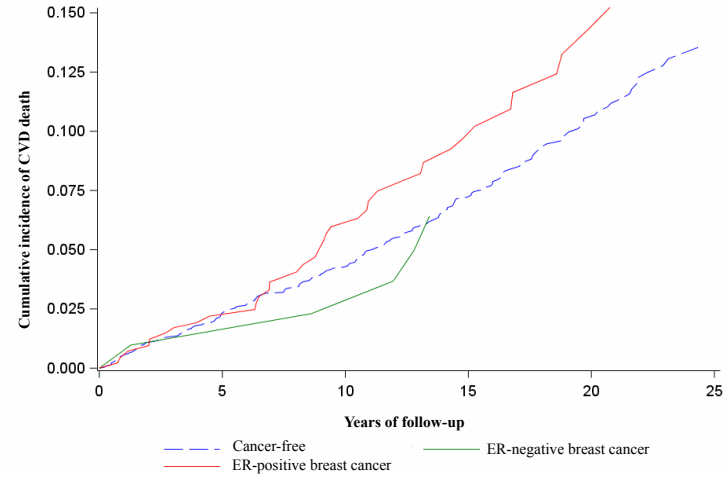
[b] The reference group is cancer-free women for HRs (95% CIs)

A



	Cancer-free	Survivors		
	Events/PT	Events/PT	csHR (95% CI)	sdHR (95% CI)
Overall				
Stage I	205/35246	29/3750	1.37 (0.93-2.02)	1.27 (0.86-1.87)
Stage II	205/35246	13/2121	1.08 (0.62-1.90)	0.93 (0.53-1.63)
Stage III	205/35246	2/283	1.33 (0.33-5.32)	0.74 (0.18-2.98)
Time since diagnosis among stage I				
0-8 years	92/20398	12/2327	1.18 (0.64-2.16)	1.16 (0.63-2.12)
>8 years	68/10228	12/1054	1.68 (0.90-3.13)	1.61 (0.87-3.00)
p-interaction			0.42	0.45

B



	Cancer-free	Survivors		
	Events/PT	Events/PT	csHR (95% CI)	sdHR (95% CI)
Overall				
ER-positive	205/35246	37/4539	1.45 (1.02-2.06)	1.28 (0.90-1.82)
ER-negative	205/35246	5/1122	0.76 (0.31-1.87)	0.63 (0.26-1.54)
Time since diagnosis among ER-positive				
0-8 years	92/20398	14/2861	1.10 (0.62-1.93)	1.06 (0.60-1.86)
>8 years	68/10228	16/1246	1.92 (1.11-3.33)	1.85 (1.06-3.20)
p-interaction			0.17	0.17

Figure 2-7. Adjusted cumulative incidence function and hazard ratios (95% confidence intervals) for cardiovascular–related mortality in breast cancer survivors stratified by (a) cancer stage and (b) estrogen-receptor status, compared with cancer-free women. Hazard ratios (95% confidence intervals) are presented overall and stratified by time since diagnosis in (a) survivors restricted to stage I cancer and (b) survivors restricted to estrogen-receptor positive tumors, compared with cancer-free women[a,b]

Abbreviations: PT, person-years; HR, hazard ratio; CI, confidence interval; IPW, inverse probability weighting
[a] Adjusted for age, menopausal status, education, smoking, alcohol use, body mass index, oral hormone use using IPW
[b] The reference group is cancer-free women for all HRs (95% CIs)

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Appendix 2

The following tables display information and results that were conducted to supplement Chapter 2.

Appendix 2-1 shows vital status characteristics as of December 31, 2015 by breast cancer status. There were a total of 916 deaths (699 in cancer-free women, 217 in breast cancer survivors). Breast cancer survivors were more likely to experience death from any cause compared to cancer-free women (34.6% vs. 22.3%). Deaths from cardiovascular disease were similar among breast cancer survivors compared to cancer-free women (7% vs. 6.5%).

Appendix 2-2 presents the list of International Disease Classification (ICD) codes used for the determination of cause-specific mortality. Among 916 deaths, 27.3% were CVD-related deaths, which were primarily due to ischemic heart disease, and 22.6% were cancer-related deaths. Other CVD-related deaths, which were not included in our primary outcome were cerebrovascular (7.2%) and essential hypertension/ hypertensive renal disease (2.3%).

Appendix 2-3 shows the HRs and 95% CIs for all-cause, CVD-related, and non-CVD-related mortality according to breast cancer status for age- and multivariable-adjusted models. Overall, results were similar in age- and multivariable-adjusted models. Here we also observed that non-CVD mortality was higher among breast cancer survivors relative to cancer-free women (csHR=2.01; 95% CI=1.69-2.40). Results using competing risk regression were similar (sdHR=1.98; 95% CI=1.66-2.36).

Appendix 2-4 presents multivariable adjusted HRs and 95% CIs for CVD-related mortality and non-CVD mortality stratified by stage and ER-status. The hazard of non-CVD mortality in breast

cancer survivors relative to cancer-free women increased with increasing stage (stage I: csHR=1.59, 95% CI=1.26-2.01; stage II: csHR=2.30, 95% CI=1.77-2.99; stage III: csHR=6.42, 95% CI=3.98-10.33). For ER-status, both women with ER-positive and ER-negative breast cancer had higher non-CVD morality relative to cancer-free women (ER-positive: csHR=1.97, 95% CI=1.61-2.40; ER-negative: csHR=2.48, 95% CI=1.73-3.54). Results were similar using competing risk regression.

Appendix 2-5 shows multivariable adjusted HRs and 95% CIs for CVD-related mortality and non-CVD mortality stratified by time since index date. Results are presented overall and restricted to stage I and ER-positive breast cancer survivors. The HR for non-CVD mortality was over 2-fold in the first 8 years but becomes attenuated after 8 years (0-8 years: csHR=2.37, 95% CI=1.85-3.03; >8 years: csHR=1.51, 95% CI=1.11-2.07; p-interaction=0.03). Results for non-CVD mortality did not differ by time in analyses restricted to stage I breast cancer compared to cancer-free women. (0-8 years: csHR=1.42, 95% CI=0.99-2.05; >8 years: csHR=1.54, 95% CI=1.05-2.26; p-interaction=0.78). Analyses restricted to ER-positive survivors compared to cancer-free women indicated that women with ER-positive breast cancer had higher non-CVD mortality in the first 8 years and results become attenuated after 8 years (0-8 years: csHR=2.13, 95% CI=1.60-2.83; >8 years: csHR=1.59, 95% CI=1.12-2.27; p-interaction=0.21). Results for these analyses were similar using competing risk regression.

Appendix 2-6 presents multivariable adjusted HRs and 95% CIs for CVD-related mortality and non-CVD mortality stratified by age at index date and jointly by age and then time since index date. Among women <70 years at index date, breast cancer survivors had higher non-CVD mortality compared to cancer-free women (csHR=2.63, 95% CI=2.02-3.41) and results are attenuated among women ≥70 years at index date (csHR=1.78, 95% CI=1.42-2.23). Among

women aged <70 years at index date, breast cancer survivors had an over 4-fold higher hazard of non-CVD mortality compared to cancer-free women in the first 8 years and results were attenuated after 8 years (0-8 years: csHR=4.16, 95% CI=2.81-6.16; >8 years: csHR=1.64, 95% CI=1.00-2.68; p-interaction=0.004). Among women aged ≥70, non-CVD mortality did not differ by time (0-8 years: csHR=1.69, 95% CI=1.22-2.35; >8 years: csHR=1.55, 95% CI=1.04-2.31; p-interaction=0.74). Results were overall similar with competing risk regression.

Appendix 2-7 shows comparisons for alternate analytic methods. Results using cox proportional hazards regression stratified by an indicator for matched set were similar to results from our primary approach (all-cause mortality: HR=1.83, 95% CI=1.58-2.11; CVD-related mortality: HR=1.24, 95% CI=0.92-1.69). Results using breast cancer as a time-varying exposure were also similar to results in our primary approach (All-cause mortality: HR=1.73, 95% CI=1.49-2.02; CVD-related mortality: HR=1.22, 95% CI=0.88-1.71).

Appendix 2-1. Vital status characteristics as of December 31, 2015 by breast cancer status

Vital status	Cancer-free women (N=3,140)	Breast cancer survivors (N=628)
Death from any cause, n (%)		
Overall	699 (22.3)	217 (34.6)
<70	242 (11.8)	92 (22.5)
≥70	637 (41.8)	125 (57.1)
Death from breast cancer, n (%)	0 (0.0)	64 (10.2)
Death from cancer (non-breast cancer), n (%)	111 (3.5)	25 (4.0)
Death from cardiovascular-related disease, n (%)	205 (6.5)	44 (7.0)

Appendix 2-2. List of International Classification of Disease (ICD) codes used for determination of cause-specific mortality (Total deaths=916)

	ICD codes	N	%
Cardiovascular disease related deaths		249	27.3
Rheumatic disease	390-398, I00-I09	3	0.003
Hypertensive diseases	402, 404, I11, I13	18	2.0
Ischemic heart disease	410-414, I20-I25	172	18.8
Pulmonary heart disease	415-417, I26-I28	8	0.01
Other forms of heart disease	420-429, I30-I51	48	5.2
Other cardiovascular disease			
Cerebrovascular	430-438, I60-I69	66	7.2
Essential hypertension, hypertensive renal disease	401,404, 405,I10, I12, I15	21	2.3
Cancer	140-208, C00-C097	207	22.6
Dementia	290, F03, G30,	86	9.4
Infection	480-487, J10-J18, 038, A40-A41	43	4.7
Diabetes	250, E10-E14	43	4.7
Pulmonary disease	490-493, 496, J40-J47	73	8.0
Deaths from all other causes	All other codes	128	14.0

Appendix 2-3. Comparison of hazard ratios (95% confidence intervals) for all-cause, cardiovascular disease, and non-cardiovascular disease mortality according to breast cancer status

	All-cause mortality		CVD mortality		Non-CVD mortality	
	Cancer-free women (deaths=699, n=3,140)	BC survivors (deaths=217, n=628)	Cancer-free women (deaths=205, n=3,140)	BC survivors (deaths=44, n=628)	Cancer-free women (deaths=494, n=3,140)	BC survivors (deaths=173, n=628)
Age-adjusted HR (95% CI)[a]	1.00 (ref)	1.76 (1.51-2.06)	1.00 (ref)	1.22 (0.88-1.69)	1.00 (ref)	1.99 (1.67-2.37)
MV-adjusted HR (95% CI)[b]	1.00 (ref)	1.79 (1.53-2.09)	1.00 (ref)	1.24 (0.89-1.72)	1.00 (ref)	2.01 (1.69-2.40)
Extended MV-adjusted HR (95% CI)[c]	1.00 (ref)	1.80 (1.54-2.10)	1.00 (ref)	1.26 (0.91-1.75)	1.00 (ref)	2.02 (1.69-2.41)
Competing risk regression						
Age-adjusted sdHR (95% CI)[a]	--	--	1.00 (ref)	1.07 (0.77-1.48)	1.00 (ref)	1.96 (1.65-2.33)
MV-adjusted sdHR (95% CI)[b]	--	--	1.00 (ref)	1.09 (0.78-1.51)	1.00 (ref)	1.98 (1.66-2.36)
Extended MV-adjusted sdHR (95% CI)[c]	--	--	1.00 (ref)	1.10 (0.80-1.53)	1.00 (ref)	1.98 (1.66-2.36)

Abbreviations: CVD, cardiovascular disease; BC, breast cancer; MV, multivariable; sdHR, subdistribution hazard ratio

Models are adjusted for covariates using inverse probability weighting

[a] Adjusted for age (years)

[b] Adjusted for age (years), menopausal status (premenopausal, postmenopausal), education (<12, 12, >12 years), smoking status (never, former, current), alcohol intake (0-3 drinks/month, ≥1 drinks/week), body mass index (<25, 25-<30,≥30 kg/m^2), oral hormone use (ever, never)

[c] Adjusted for age (years), menopausal status (premenopausal, postmenopausal), education (<12, 12, >12 years), smoking status (never, former, current), alcohol intake (0-3 drinks/month, ≥1 drinks/week), body mass index (<25, 25-<30, ≥30 kg/m^2), oral hormone use (ever, never), high blood pressure (yes, no), high cholesterol (yes, no), cardiovascular medication (yes, no), diabetes medication (yes, no)

Appendix 2-4. Hazard ratios (95% confidence intervals) for cardiovascular disease and non-cardiovascular disease mortality in breast cancer survivors stratified by tumor characteristics compared to cancer-free women

	CVD mortality				Non-CVD mortality			
	Deaths/person-years		csHR (95% CI)[a,b]	sdHR (95% CI)[a,b]	Deaths/person-years		csHR (95% CI)[a,b]	sdHR (95% CI)[a,b]
	Cancer-free women	BC survivors			Cancer-free women	BC survivors		
Stage at diagnosis								
Stage I	205/35,246	29/3,750	1.37 (0.93-2.02)	1.27 (0.86-1.87)	494/35,246	83/3,803	1.59 (1.26-2.01)	1.55 (1.23-1.96)
Stage II	205/35,246	13/2,121	1.08 (0.62-1.90)	0.93 (0.53-1.63)	494/35,246	67/2,130	2.30 (1.77-2.99)	2.28 (1.76-2.97)
Stage III	205/35,246	2/283	1.33 (0.33-5.32)	0.74 (0.18-2.98)	494/35,246	20/280	6.42 (3.98-10.33)	6.01 (3.69-9.80)
ER-status								
ER-positive	205/35,246	37/4,539	1.45 (1.02-2.06)	1.28 (0.90-1.82)	494/35,246	121/4,614	1.97 (1.61-2.40)	1.91 (1.56-2.33)
ER-negative	205/35,246	5/1,122	0.76 (0.31-1.87)	0.63 (0.26-1.54)	494/35,246	39/1,128	2.48 (1.73-3.54)	2.51 (1.80-3.58)

Abbreviations: CVD, cardiovascular disease; BC, breast cancer; csHR, cause-specific hazard ratio; sdHR, subdistribution hazard ratio

[a] The reference group for all models is cancer-free women

[b] Adjusted for age (years), menopausal status (premenopausal, postmenopausal), education (<12, 12, >12 years), smoking status (never, former, current), alcohol intake (0-3 drinks/month, ≥1 drinks/week), body mass index (<25, 25-<30, ≥30 kg/m^2), oral hormone use (ever, never) using inverse probability weighting

Appendix 2-5. Hazard ratios (95% confidence intervals) for cardiovascular disease and non-cardiovascular disease mortality according to breast cancer status stratified by time since diagnosis

Time since diagnosis	CVD mortality				Non-CVD mortality			
	Deaths/person-years		csHR (95% CI) [a,b]	sdHR (95% CI) [a,b]	Deaths/person-years		csHR (95% CI) [a,b]	sdHR (95% CI) [a,b]
	Cancer-free women	BC survivors			Cancer-free women	BC survivors		
Overall								
0-8 years	92/20,398	17/3,875	0.99 (0.59-1.66)	0.94 (0.56-1.58)	210/20,398	93/3,875	2.37 (1.85-3.03)	2.36 (1.85-3.02)
>8 years	68/10,228	20/1,744	1.71 (1.03-2.83)	1.65 (1.00-2.73)	192/10,228	50/1,744	1.51 (1.11-2.07)	1.48 (1.09-2.03)
p-interaction[c]			0.14	0.13			0.03	0.02
Stage I								
0-8 years	92/20,398	12/2,327	1.18 (0.64-2.16)	1.16 (0.63-2.12)	210/20,425	34/2,311	1.42 (0.99-2.05)	1.42 (0.98-2.04)
>8 years	68/10,228	12/1,054	1.68 (0.90-3.13)	1.61 (0.87-3.00)	192/10,264	31/1,030	1.54 (1.05-2.26)	1.52 (1.03-2.23)
p-interaction[c]			0.42	0.45			0.78	0.8
ER-positive								
0-8 years	92/20,398	14/2,861	1.10 (0.62-1.93)	1.06 (0.60-1.86)	210/20,425	62/2,838	2.13 (1.60-2.83)	2.13 (1.60-2.83)
>8 years	68/10,228	16/1,246	1.92 (1.11-3.33)	1.85 (1.06-3.20)	192/10,264	37/1,217	1.59 (1.12-2.27)	1.55 (1.09-2.21)
p-interaction[c]			0.17	0.17			0.21	0.17

Abbreviations: CVD, cardiovascular disease; BC, breast cancer; csHR, cause-specific hazard ratio; sdHR, subdistribution hazard ratio; ER, estrogen-receptor

[a] The reference group for all models is cancer-free women

[b] Adjusted for age (years), menopausal status (premenopausal, postmenopausal), education (<12, 12, >12 years), smoking status (never, former, current), alcohol intake (0-3 drinks/month, ≥1 drinks/week), body mass index (<25, 25-<30, ≥30 kg/m^2), oral hormone use (ever, never) using inverse probability weighting

[c] P-interaction for the cross-product term of breast cancer status and time

Appendix 2-6. Hazard ratios (95% confidence intervals) for cardiovascular disease and non-cardiovascular disease mortality according to breast cancer status stratified by age at diagnosis and the joint association of age at diagnosis and time since diagnosis

	CVD mortality				Non-CVD mortality			
	Deaths/person-years		csHR (95% CI)[a,b]	sdHR (95% CI)[a,b]	Deaths/person-years		csHR (95% CI)[a,b]	sdHR (95% CI)[a,b]
	Cancer-free women	BC survivors			Cancer-free women	BC survivors		
Age at diagnosis								
Age <70 years	56/25,740	7/4,611	0.77 (0.35-1.70)	0.68 (0.31-1.49)	186/25,670	85/4662	2.63 (2.02-3.41)	2.64 (2.03-3.43)
Age ≥70 years	149/9,597	37/1,660	1.58 (1.10-2.27)	1.25 (0.87-1.80)	308/9,576	88/1672	1.78 (1.42-2.23)	1.59 (1.26-2.00)
p-interaction[c]			0.11	0.18			0.01	0.01
Time and age								
Age <70 years								
0-8 years	19/13,821	1/2,627	0.35 (0.05-2.6)	0.34 (0.05-2.51)	58/13,821	45/2627	4.16 (2.81-6.16)	4.16 (2.81-6.16)
>8 years	20/7,864	2/1,374	0.53 (0.12-2.26)	0.51 (0.12-2.19)	72/7,864	21/1374	1.64 (1.00-2.68)	1.65 (1.01-2.70)
p-interaction[c]			0.75	0.74			0.004	0.004
Age ≥70 years								
0-8 years	73/6,577	16/1,248	1.16 (0.67-1.98)	1.10 (0.64-1.88)	152/6,577	48/1248	1.69 (1.22-2.35)	1.67 (1.20-2.31)
>8 years	48/2,364	18/370	2.43 (1.40-4.21)	2.24 (1.29-3.88)	120/2,364	29/370	1.55 (1.04-2.31)	1.40 (0.94-2.09)
p-interaction[c]			0.06	0.07			0.74	0.48

Abbreviations: CVD, cardiovascular disease; BC, breast cancer; csHR, cause-specific hazard ratio; sdHR, subdistribution hazard ratio

[a] The reference group for all models is cancer-free women

[b] Adjusted for age (years), menopausal status (premenopausal, postmenopausal), education (<12, 12, >12 years), smoking status (never, former, current), alcohol intake (0-3 drinks/month, ≥1 drinks/week), body mass index (<25, 25-<30, ≥30 kg/m^2), oral hormone use (ever, never) using inverse probability weighting

[c] P-interaction for the cross-product term of breast cancer status and listed categories

Appendix 2-7. Comparison of hazard ratios (95% confidence intervals) for all-cause and cardiovascular disease mortality according to breast cancer status using alternative analytic approaches

	All-cause mortality		CVD mortality	
	Cancer-free women (deaths=699, n=3,140)	BC survivors (deaths=217, n=628)	Cancer-free women (deaths=205, n=3,140)	BC survivors (deaths=44, n=628)
Model A HR (95% CI)[a,b]	1.00 (ref)	1.83 (1.58-2.11)	1.00 (ref)	1.24 (0.92-1.69)
Model B HR (95% CI)[a,c]	1.00 (ref)	1.73 (1.49-2.02)	1.00 (ref)	1.22 (0.88-1.71)

Abbreviations: CVD, cardiovascular disease; BC, breast cancer

[a] Adjusted for age (years), menopausal status (premenopausal, postmenopausal), education (<12, 12, >12 years), smoking status (never, former, current), alcohol intake (0-3 drinks/month, ≥1 drinks/week), body mass index (<25, 25-<30, ≥30 kg/m^2), oral hormone use (ever, never) using inverse probability weighting

[b] Models are stratified by matched set

[c] Breast cancer status is a time-varying exposure

Chapter 3.

Incident cardiovascular disease risk factors in breast cancer survivors compared to cancer-free women in a familial risk cohort

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Abstract

Background: Cardiovascular disease (CVD) morbidity and mortality is an issue of increasing concern among breast cancer survivors. Several modifiable risk factors including hypertension, elevated blood lipids, and diabetes have been commonly reported in breast cancer survivors and may represent a crucial early point of intervention to improve long-term CVD health. However, whether breast cancer survivors have an increased risk of incident CVD risk factors relative to cancer-free women and whether these risk factors develop shortly after diagnosis remains unknown.

Methods: We prospectively examined the incidence of hypertension, high cholesterol, high triglycerides, and diabetes in breast cancer survivors compared to cancer-free women in the Breast and Ovarian Surveillance Service (BOSS) study, an ongoing familial risk cohort. Survivors were diagnosed with ductal carcinoma *in situ* or stage I-IV breast cancer ≤5 years prior to baseline (N=304). Cancer free women were defined as women with no prior history of cancer at baseline (except non-melanoma skin cancer or cervical carcinoma *in situ*) (N=742). Breast cancer and tumor characteristics were confirmed with pathology records. Incident CVD risk factors were ascertained based on self-reported physician diagnosis. Multivariable hazard ratios (HR) and 95% confidence intervals (CI) for CVD risk factors were calculated using Cox proportional hazard regression models.

Results: Breast cancer survivors were diagnosed, on average, 1.4 years prior to study enrollment and the mean age at diagnosis ranged from 47-49 years. Overall, in multivariable models, breast cancer survivors did not have a higher risk of hypertension, high cholesterol, or diabetes. An increased risk of developing high triglycerides was observed in breast cancer survivors relative to

cancer free women (HR=3.96, 95% CI=1.85-8.51) and, although not significant, there was a suggestion that risk of high triglycerides may differ by BMI subgroups (p-interaction=0.10). Risk of hypertension was increased in breast cancer survivors diagnosed at age ≤50 relative to cancer-free women (HR=2.04, 95% CI=1.04-4.00), although no association was observed in survivors diagnosed at age >50 years compared to cancer-free women (HR=0.76, 95% CI=0.33-1.77).

Conclusion: Our study suggests that closer monitoring of triglyceride levels among all breast cancer survivors and blood pressure among women diagnosed with breast cancer at age ≤50 years is warranted.

Introduction

Cardiovascular disease (CVD) is an established long-term risk after breast cancer[1] and represents the leading cause of non-cancer death among breast cancer survivors in the United States.[2] Several modifiable risk factors including hypertension, elevated blood lipids, and diabetes have been commonly reported in breast cancer survivors and may represent a crucial point for early intervention to reduce the long-term risk of CVD.[3] However, the development of CVD risk factors in breast cancer survivors is likely multifactorial as it is related to both breast cancer and its treatment as well as age, menopausal status, and lifestyle factors (e.g., obesity and physical inactivity).[4,5]

Among breast cancer survivors, the direct effects of treatment on CVD risk have been well established (e.g., radiation induced cardiovascular injury and cardiotoxic effects of systemic therapies).[3,6] In addition, breast cancer treatment has been linked to small yet unfavorable changes in blood pressure[6-11] and blood lipids,[12-16] and an increased risk of diabetes.[3,17] Treatment-related early menopause, which lowers endogenous estrogen levels, may also increase weight gain and subsequently lead to unfavorable metabolic changes.[1] Importantly, hypertension, elevated blood lipids, and diabetes are also prevalent in cancer-free women due to factors such as obesity, unhealthy diet, physical inactivity, and family history.[18] Therefore, these factors may also contribute to the development of CVD in breast cancer survivors in addition to treatment related effects.

Several prior studies have reported a higher prevalence of CVD risk factors in long-term breast cancer survivors relative to cancer-free women[19,20] and one study has reported that adolescent and

young adult breast cancer survivors are more likely to develop CVD risk factors compared to cancer-free individuals.[21] However, to our knowledge, no prior study has examined incident CVD risk factors in adult breast cancer survivors compared to cancer-free women. Therefore, it remains unclear whether breast cancer survivors, particularly those that are recently diagnosed, are more likely to develop CVD risk factors than their cancer-free peers and to what degree age, menopause, and lifestyle factors confound this association.

To examine the risk of hypertension, high cholesterol, high triglycerides, and diabetes in recently diagnosed breast cancer survivors compared to cancer-free women, we analyzed data from women with familial breast cancer risk in the Breast and Ovarian Surveillance Service (BOSS) study.

Methods

Study population

The Breast and Ovarian Surveillance Service (BOSS) study is an ongoing prospective cohort study, which recruited women and men with familial risk for breast and/or ovarian cancer in 2005-2013 from the cancer genetics clinic at the John Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland. Eligible participants were aged ≥18 years with either: 1) a family history of breast and/or ovarian cancer, 2) a documented BRCA1/2 mutation, 3) a diagnosis with breast cancer at ≤40 years of age without a family history of breast cancer, or 4) a diagnosis with ovarian cancer at any age without a family history of ovarian cancer. At baseline, participants completed a detailed questionnaire to collect information on a variety of demographic, lifestyle, and health factors including information on medical history and breast

cancer treatment. Participants have updated their information every 3-4 years thereafter with follow-up questionnaires (>92% have completed at least 1 follow-up questionnaire).

For the present analysis, women were included if they completed a baseline questionnaire and at least 1 follow-up questionnaire through December 31st, 2017 (n=1,178). Breast cancer survivors were defined as women diagnosed with breast cancer (ductal carcinoma *in situ* or stage I-IV breast cancer) within 5 years prior to enrollment (n=304). The comparison group was restricted to women with no prior history of cancer at baseline except non-melanoma skin cancer or cervical carcinoma *in situ* (N=742). Women who reported a physician diagnosis for hypertension, high cholesterol, high triglycerides, or diabetes at baseline were excluded from analyses for that risk factor. We further excluded women with missing responses on baseline or follow-up questionnaires from analyses for that risk factor (n=3 for hypertension; n=3 for high cholesterol; n=7 for high triglycerides; n=1 for diabetes). After these exclusions, our analytic populations ranged from 675 to 922 women.

Ascertainment of breast cancer and treatment

Breast cancer was self-reported at enrollment and pathology records were used to confirm all diagnoses (International Classification of Disease-10 code: invasive breast cancer [C50]; ductal carcinoma *in situ* [D05.1] and lobular carcinoma *in situ* [D05.0]). Breast cancer stage and subtype (estrogen/progesterone receptor and HER2 status) was also confirmed with pathology reports. Breast cancer treatment was ascertained in baseline questionnaires and confirmed with medical record review (99% confirmed for the present analysis). Treatment information included surgery (none, lumpectomy, mastectomy), and adjuvant therapy (chemotherapy, radiation, and hormonal therapy).

Ascertainment of CVD risk factors

Physician diagnosed CVD risk factors including high blood pressure (excluding during pregnancy), high cholesterol, high triglycerides, and diabetes were ascertained in baseline and follow-up questionnaires. In each questionnaire, participants were asked to indicate whether they had received a physician's diagnosis and the date of diagnosis. Incident cases of hypertension, high cholesterol, high triglycerides and diabetes were identified on follow-up questionnaires. We did not include weight gain as a CVD risk factor in this analysis since it was previously established in this cohort that weight gain was higher in cancer survivors relative to cancer-free women.[22]

Ascertainment of covariates

Information on covariates [age, race, education level, menopausal status, age at menopause, oophorectomy at a young age, body mass index (BMI), physical activity based on metabolic equivalents of task (METs) per week, alcohol intake, smoking status, hormonal replacement therapy (HRT) use, and history of screening (mammography, pap smear)] was collected from the baseline questionnaire. Removal of the ovaries was based on self-report and confirmation with pathology records is ongoing. We defined a bilateral oophorectomy at a young age as the removal of both ovaries prior to age 45 years.

Statistical analysis

We calculated age-adjusted means and proportions for baseline characteristics in breast cancer survivors and cancer-free women using regression modeling. We used Cox proportional hazard models to estimate age- and multivariable-adjusted hazard ratios (HRs) of incident CVD risk

factors with 95% confidence intervals (CIs). We used age as the time scale in our models.[23] Women contributed person-time from the completion date of the baseline questionnaire to the date of diagnosis for a CVD risk factor or until end of last follow-up through December 31st, 2017, whichever occurred first. The proportional hazards assumption between all covariates and CVD risk factors was assessed with Schoenfeld residuals and indicated that the assumption of proportional hazards was not violated. We identified confounders *a priori* as variables that may be associated with both breast cancer incidence and CVD risk factors. Our primary multivariable model adjusted for race (white, other), education status (<4 years of college, ≥4 years of college), menopausal status (premenopausal, postmenopausal), hormone replacement therapy (ever, never), body mass index (BMI) (kg/m^2), physical activity (MET-h/week), smoking status (ever, never) and alcohol use (g/day). A second multivariable model mutually adjusted for the other CVD risk factors to examine the independent effect of each CVD risk factor. Overall, results were similar between these two models, therefore we discuss model results from the more parsimonious model that did not mutually adjust for other CVD risk factors. Due to a small percent of missing values for covariates included in multivariable models (<1% missing), we imputed missing data with the most common category for categorical covariates and the median value for continuous covariates among cancer-free women.

We conducted a number of sensitivity analyses. First, we excluded women diagnosed with stage 0 or stage IV breast cancer from our primary analyses since treatment may differ in these groups compared to women with stage I-III breast cancer. Second, we excluded women with an early bilateral oophorectomy prior to baseline. We excluded these women since early bilateral oophorectomy is associated with CVD mortality and therefore women still alive and healthy at baseline may represent a unique population. Finally, we excluded women with a change in menopause over follow-up to determine if menopause, either natural or treatment-related, might be driving the development of incident CVD risk factors.

We further examined the risk of hypertension, high cholesterol, and high triglycerides in women with breast cancer stratified by age at diagnosis, menopausal status at diagnosis, and estrogen-receptor (ER) tumor status to determine if the association may differ by these factors. Models that stratified survivors by ER-status were restricted to invasive cancer since this information has not been routinely measured, until recently, in women with *in situ* breast cancer. We were unable to examine incident diabetes for these subgroup analyses and the effects of breast cancer treatment on the development of CVD risk factors due to small numbers. Finally, we conducted stratified analyses to determine whether associations between breast cancer status and incident CVD risk factors differed by baseline BMI. Heterogeneity was tested using the likelihood ratio test.

Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 14.0 (StataCorp LP, College Station, TX, USA). All statistical tests were two-side and P values ≤0.05 were considered statistically significant.

Results

Table 3-1 describes age and age-adjusted characteristics at baseline for each analytic population according to breast cancer status. Overall, characteristics were similar among breast cancer survivors compared to cancer-free women. However, breast cancer survivors tended to be older and postmenopausal and were less likely to be white compared to cancer-free women. In addition, both groups were highly educated with approximately 80% of women with ≥4-years of college. Among breast cancer survivors, the mean time from diagnosis to enrollment was 1.4 years and the mean age at diagnosis ranged from 47-49 years. Breast cancer survivors were primarily diagnosed with invasive breast cancer and ER-positive breast tumors. For breast cancer treatment,

all survivors received surgery (excluding women with stage IV breast cancer) and approximately 50% received chemotherapy. In addition, over 65% of breast cancer survivors received any hormone therapy.

Table 3-2 describes risk of hypertension, elevated blood lipids, and diabetes among breast cancer survivors relative to cancer-free women. Breast cancer status was not significantly associated with incident hypertension, high cholesterol, and diabetes. However, risk of high triglycerides was almost 4-fold higher in breast cancer survivors relative to cancer-free women (HR=3.96, 95% CI=1.85-8.51). Results were similar in models that mutually adjusted for other CVD risk factors. In sensitivity analyses, we excluded women with stage 0 or stage IV breast cancer from our models and overall results were comparable to our primary analyses. Results that excluded women with an early bilateral oophorectomy were also generally similar to our primary analyses; however, the magnitude of risk for incident high triglycerides was even stronger in this model. Results that excluded women with a change in menopause over follow-up were attenuated suggesting that becoming post-menopausal may play a role in the development of CVD risk factors. However, results for incident high triglycerides remained statistically significant suggesting that other factors may also play a role in the development of this risk factor (HR=2.74, 95% CI=1.13-6.63).

Table 3-3 examines CVD risk factors in breast cancer survivors stratified by age at diagnosis, menopausal status at diagnosis, and ER-status compared to cancer-free women. Overall, women diagnosed at a younger age had a higher risk of hypertension compared to cancer-free women. Specifically, women diagnosed with breast cancer at age ≤50 years had a 2-fold increased risk of hypertension compared to cancer-free women (HR=2.04; 95% CI=1.04-4.00). No increased risk of hypertension was observed in survivors diagnosed at age >50 years compared to cancer-free women (HR=0.76, 95% CI=0.33-1.77). In addition, risk of high triglycerides remained increased

among breast cancer survivors relative to cancer-free women in all models and did not differ by age or menopausal status at diagnosis. Risk of elevated triglycerides was over 7-fold higher among women with ER-negative breast cancer and over 3-fold higher among women with ER-positive tumors (HR=7.61, 95% CI=2.50-23.17, HR=3.29, 95% CI=1.34-8.07, respectively).

We then examined the findings by subgroups of BMI at baseline (BMI<25 kg/m^2, BMI≥25 kg/m^2) (Table 3-4). Results did not differ by BMI status for incident hypertension and high cholesterol. However, there was a suggestion that risk of high triglycerides differed by baseline BMI status (p-interaction=0.10). Specifically, women with breast cancer had an almost 8-fold and over 2-fold increased risk of high triglycerides relative to cancer-free women among overweight/obese women and normal weight women, respectively (HR=7.88, 95% CI=2.61-23.79; HR=2.20, 95% CI=0.69-7.04).

Discussion

In this prospective study, we observed an increased risk of high triglycerides in breast cancer survivors relative to cancer-free women particularly among overweight/obese women. We found no overall association between breast cancer status and incident hypertension, high cholesterol, or diabetes. However, we observed that women diagnosed with breast cancer at age ≤50 years may have an increased risk of hypertension compared to cancer-free women. These findings highlight the need to mitigate CVD risk factors early after diagnosis to reduce the long-term risk of CVD in breast cancer survivors.

Although several studies have reported a higher prevalence of CVD risk factors in breast cancer survivors compared to cancer-free women,[19,20] this study is the first, to our knowledge, to

examine incident CVD risk factors in adult breast cancer survivors compared to cancer-free women. One previous study examined incident CVD risk factors, as well as incident CVD, among adolescent and young adult (AYA) cancer survivors (aged 15-39 years at diagnosis; n=963 breast cancer survivors) compared to an age- and sex-matched group without cancer (n=57,617) in the Kaiser health care system.[21] After 4.1 mean years of follow-up, this study found that breast cancer survivors had a higher incidence of diabetes and dyslipidemia compared to cancer-free women after adjusting for age, ethnicity, smoking, and BMI (IRR=1.55, 95% CI=1.20-2.02; IRR=1.20, 95% CI=1.01-1.43, respectively). This study found no association between breast cancer status and hypertension (IRR=1.06; 95% CI=0.86-1.32). Our study was conducted among adult breast cancer survivors (mean age at diagnosis=47-49 years) and therefore there may be important differences in breast cancer characteristics (i.e., stage and tumor subtype) and thus subsequent treatment compared to the Kaiser population of AYA survivors. The authors did not report clinical cancer information on stage, subtype, or treatment; therefore it is hard to determine if this may be driving the differences in results between studies. Furthermore, risk of hypertension, high blood lipids, and diabetes may differ substantially among adult women compared to AYA women since development of these factors is also highly associated with increasing age and menopausal status. In addition, we analyzed high cholesterol and triglycerides as individual outcomes and it is unclear if high triglycerides were included in the composite outcome of dyslipidemia in the Kaiser study. It is also possible that our analyses were underpowered to detect the modest association with diabetes that was observed in the Kaiser population of AYA survivors.

We are the first prospective study to report that breast cancer survivors may have an increased risk of high triglycerides compared to cancer-free women after accounting for the effects of age and menopause, which are strong confounders. Furthermore, this association persisted after adjustment for other CVD risk factors including hypertension, diabetes, and high cholesterol and

in additional sensitivity analyses. This suggests that the underlying etiology may be related to breast cancer and its treatment. Although tamoxifen has been shown to decrease total and low-density lipoprotein (LDL) cholesterol levels,[24,25] previous clinical studies have also shown that tamoxifen use may increase serum triglycerides.[12,13] While the mechanisms underlying this association are unknown, it is hypothesized that estrogen may be protective and therefore lowering tamoxifen dosage may reduce the risk of hypertriglyceridemia.[13] Future studies are needed to confirm if tamoxifen use or other breast cancer treatments may be driving the increased risk of high triglycerides among breast cancer survivors relative to cancer-free women and whether there is a long-term increased risk. Further studies are also needed to confirm our finding that the elevation in triglycerides may be greater in overweight/obese women.

We are also the first study to find that breast cancer survivors diagnosed at age ≤50 years (mean age at diagnosis=42 years) had a higher risk of hypertension compared to cancer-free women. Although this finding needs to be confirmed with repeated measurements and in larger studies, it is possible that this increased risk may be due to either direct or indirect effects of treatment. Hypertension has been commonly reported in breast cancer patients treated with selected angiogenesis inhibitors.[6,26-28] Specifically, Bevacizumab, an angiogenesis inhibitor that was approved for the treatment of metastatic HER2-negative breast cancer from 2008-2011, has been associated with an increased risk of hypertension.[8,28] However, this is unlikely to explain the observed association in our analysis since only 2 women diagnosed at age ≤50 years had this treatment and neither developed incident hypertension. It is also possible that women diagnosed at a younger age may be more likely to receive chemotherapy due to aggressive tumor biology associated with a younger age at diagnosis. Indeed, in this analysis, women diagnosed at ≤50 years were slightly more likely to receive chemotherapy compared to women diagnosed at >50 years (52% vs. 45%, respectively). Chemotherapy, particularly anthracyclines and cisplatin, has been shown to cause vascular endothelial damage, and has been associated with hypertension in

cancer patients.[7,26,29] Further work is ongoing to determine if younger women in our study were more likely to receive anthracycline chemotherapy agents. In addition, chemotherapy can induce treatment-related early menopause and lower levels of endogenous estrogen may subsequently cause unfavorable changes in blood pressure and increases in weight gain, which may also play a role in the development of hypertension.[1]

The strengths of this study include the prospective design and a direct comparison to cancer-free women from the same cohort. However, our study also has several limitations. First, our sample size was limited and our analyses were underpowered to detect significant small to moderate associations. We were also unable to examine treatment effects due to our limited sample size. However, we are the first study to examine incident CVD risk factors in adult breast cancer survivors relative to cancer-free women within the same cohort. Larger studies are needed to replicate our findings and to examine treatment effects. Second, incident CVD risk factors were based on self-reported physician diagnosis, therefore we can not rule out the potential for outcome misclassifiction. However, women in the BOSS cohort are at high risk for familail breast cancer and thus both breast cancer survivors and cancer-free women routinely undergo health assessments. In addition, health screening exams reported at baseline were similar by breast cancer status and therefore it is unlikely that self-reported outcomes might differ by exposure group. Third, our results may lack generalizability to other populations since our study population was comprised of predominately white and highly-educated women with a family history of breast cancer. Future studies are needed in other diverse study populations.

In conclusion, breast cancer survivors had an increased risk of high triglycerides relative to cancer-free women and survivors diagnosed at age ≤50 years may be at increased risk of hypertension. This study suggests that early post-diagnostic monitoring of CVD risk factors may

be warranted even in younger breast cancer survivors to reduce long-term CVD risk. Future longitudinal studies are needed to confirm these results.

Table 3-1. Age and age-adjusted baseline characteristics of cancer-free women and breast cancer survivors in the BOSS cohort study

Characteristic	**Hypertension (N=777)**		**High cholesterol (N=675)**		**High triglycerides (N=828)**		**Diabetes (N=922)**	
	Cancer-free (n= 561)	Survivors[a] (n=216)	Cancer-free (n=488)	Survivors[a] (n=187)	Cancer-free (n=597)	Survivors[a] (n=231)	Cancer-free (n=661)	Survivors[a] (n=261)
Age, mean years (SD)	45.0(11.2)*	49.0(10.5)*	44.7(11.4)*	48.5(10.5)*	45.8(11.9)*	49.7(10.8)*	46.7(11.9)*	50.5(11.0)*
White, %	91.7*	83.3*	90.0*	79.8*	89.7*	81.6*	90.7*	82.7*
Education, ≥4-year college, %	79.8	82.9	78.9	82.8	76.8	80.7	78.4	80.8
Postmenopausal, %	32.7*	49.0*	30.7*	46.8*	35.7*	50.6*	38.2*	53.0*
Age at menopause[b], mean years (SD)	48.9(6.8)	49.7(4.7)	49.3(5.3)	50.1(4.5)	49.0(6.6)	50.1(4.2)	49.0(6.6)	50.0(4.7)
Bilateral oophorectomy at age <45 years[c], %	44.5	31.2	43.0	28.9	45.9*	21.3*	45.5*	24.9*
BMI, mean kg/m^2 (SD)	25.2(5.2)	24.9(5.3)	25.2(5.6)	25.2(5.8)	25.5(5.7)	25.1(5.7)	25.8(5.7)	25.3(5.4)
Physical activity, mean MET-h/week[d] (SD)	30.6(31.6)	27.5(31.3)	31.0(33.0)	26.7(32.2)	29.7(31.9)	27.3(32.2)	29.0(30.8)	26.8(30.8)
Alcohol intake, mean g/day (SD)	6.0(8.9)	5.6(8.7)	5.8(8.1)	6.4(9.9)	5.8(8.3)	6.0(9.6)	6.1(9.1)	5.9(9.5)
Smoking status, %								
Never	59.6	57.4	63.0	60.1	60.8	57.4	59.2	55.2
Former	35.9	39.7	33.6	37.8	35.1	40.5	36.8	42.0
Current	4.2	2.5	3.2	1.7	3.8	1.7	3.7	2.5
Missing	0.2	0.4	0.2	0.5	0.4	0.4	0.3	0.3
Hormone replacement therapy ever use, %	18.2	15.2	17.1	16.2	18.6	17.7	20.8	18.6
Ever mammogram[e], %	98.4	98.0	98.1	97.6	98.6	98.2	98.8	98.5
Ever pap smear, %	98.4	98.9	99.0	98.7	98.8	98.9	98.7	98.8
High cholesterol, %	23.1	23.0	--	--	20.4	19.4	28.5	27.9
High blood pressure, %	--	--	10.9	12.3	15.7	14.8	17.9	17.4
High triglycerides, %	10.0	9.4	2.0	2.5	--	--	13.2	10.3
Diabetes, %	2.5	2.5	2.3	2.2	3.5	1.2	--	--
Age at diagnosis, mean years (SD)	--	47.5(10.4)	--	47.1(10.4)	--	48.3(10.7)	--	49.1(10.9)
Time from diagnosis to baseline, mean years (SD)	--	1.4(1.3)	--	1.4(1.3)	--	1.4(1.3)	--	1.4 (1.3)
Breast cancer stage, %								

Stage 0	--	17.1	--	16.0	--	17.8	--	17.6
Stage I-III	--	81.0	--	83.4	--	81.0	--	80.8
Stage IV	--	1.9	--	<1	--	1.3	--	1.5
Estrogen receptor status[f], %	--		--		--		--	
Positive	--	76.5	--	78.3	--	77.9	--	78.6
Negative	--	22.9	--	21.7	--	21.6	--	20.9
Missing/untested	--	<1	--	0	--	<1	--	<1
Breast cancer treatment[g], %	--		--		--		--	
Surgery[h]	--	100.0	--	100.0	--	100.0	--	100.0
Chemotherapy	--	49.5	--	53.5	--	50.7	--	49.0
Hormonal therapy, any	--	64.8	--	65.2	--	66.2	--	66.3
Hormonal therapy, by type	--		--		--		--	
Tamoxifen	--	70.0	--	67.2	--	66.0	--	63.6
Aromatase inhibitor	--	39.3	--	40.2	--	42.5	--	44.5

Values are means(SD) or percentages and are age-adjusted

* $p<0.05$

[a] Women were diagnosed with stage 0-IV breast cancer ≤5 years prior to baseline

[b] Among post-menopausal women

[c] Among women who had both ovaries removed (n=72)

[d] Metabolic equivalents from recreational and occupational activity

[e] Among women aged ≥50 years

[f] Among invasive cases only (n=179 for hypertension; n=157 for high cholesterol; n=192 for high triglycerides; n=215 for diabetes)

[g] Treatment groups are not mutually exclusive and treatment with chemotherapy and hormonal therapy is adjuvant

[h] Excluding women with stage IV breast cancer

Table 3-2. Hazard ratios and 95% confidence intervals for incident cardiovascular disease risk factors among breast cancer survivors compared to cancer-free women (continued on next page)

	Hypertension (N=777)				**High cholesterol (N=675)**			
	Events/ person-years	Age-adjusted HR (95% CI)	MV-adjusted HR[a] (95% CI)	MV-adjusted HR + CVD risk factors[b] (95% CI)	Events/ person-years	Age-adjusted HR (95% CI)	MV-adjusted HR[a] (95% CI)	MV-adjusted HR + CVD risk factors[b] (95% CI)
Overall								
Cancer-free	45/3696	1.00 (ref)	1.00 (ref)	1.00 (ref)	50/3177	1.00 (ref)	1.00 (ref)	1.00 (ref)
Survivor	20/1265	1.12 (0.66-1.90)	1.31 (0.76-2.26)	1.32 (0.76-2.28)	21/1077	1.07 (0.64-1.78)	1.02 (0.60-1.73)	1.03 (0.61-1.75)
Sensitivity analyses								
Excluding stage 0 breast cancer								
Cancer-free	45/3696	1.00 (ref)	1.00 (ref)	1.00 (ref)	50/3177	1.00 (ref)	1.00 (ref)	1.00 (ref)
Survivor	15/1038	1.01 (0.56-1.82)	1.17 (0.63-2.16)	1.16 (0.63-2.14)	19/882	1.16 (0.68-1.98)	1.09 (0.63-1.90)	1.10 (0.64-1.91)
Excluding stage IV breast cancer								
Cancer-free	45/3696	1.00 (ref)	1.00 (ref)	1.00 (ref)	50/3177	1.00 (ref)	1.00 (ref)	1.00 (ref)
Survivor	19/1242	1.08 (0.63-1.85)	1.27 (0.73-2.22)	1.29 (0.74-2.26)	21/1074	1.07 (0.64-1.79)	1.02 (0.60-1.73)	1.03 (0.61-1.75)
Excluding early bilateral oophorectomy								
Cancer-free	42/3540	1.00 (ref)	1.00 (ref)	1.00 (ref)	46/3089	1.00 (ref)	1.00 (ref)	1.00 (ref)
Survivor	20/1163	1.23 (0.72-2.11)	1.39 (0.80-2.42)	1.45 (0.83-2.54)	18/1024	1.00 (0.57-1.73)	1.00 (0.57-1.75)	0.98 (0.56-1.73)
Excluding pre- to post-menopausal								
Cancer-free	35/2477	1.00 (ref)	1.00 (ref)	1.00 (ref)	33/2147	1.00 (ref)	1.00 (ref)	1.00 (ref)
Survivor	11/924	0.68 (0.34-1.36)	0.82 (0.40-1.67)	0.81 (0.39-1.64)	15/739	1.04 (0.56-1.94)	0.89 (0.46-1.71)	0.92 (0.48-1.77)

Abbreviations: CVD, cardiovascular disease; MV, multivariable

[a]Model adjusted for age (years), race (white, other), education status (≥4-year college, <4-year college), menopausal status at baseline (premenopausal, postmenopausal), body mass index (kg/m^2), physical activity (MET-h/week), smoking status (never, ever), alcohol intake (grams/day) and hormone replacement therapy (never, ever)

[b]Model mutually adjusted for other CVD risk factors: hypertension, high cholesterol, high triglycerides, and diabetes

Table 3-2. Hazard ratios and 95% confidence intervals for incident cardiovascular disease risk factors in breast cancer survivors compared to cancer-free women

	High triglycerides (N=828)				**Diabetes (N=922)**			
	Events/ person-years	Age-adjusted HR (95% CI)	MV-adjusted HR[a] (95% CI)	MV-adjusted HR + CVD risk factors[b] (95% CI)	Events/ person-years	Age-adjusted HR (95% CI)	MV-adjusted HR[a] (95% CI)	MV-adjusted HR + CVD risk factors[b] (95% CI)
Overall								
Cancer-free	12/4071	1.00 (ref)	1.00 (ref)	1.00 (ref)	21/4494	1.00 (ref)	1.00 (ref)	1.00 (ref)
Survivor	18/1388	3.99 (1.90-8.41)	3.96 (1.85-8.51)	4.00 (1.85-8.64)	5/1623	0.64 (0.24-1.72)	0.68 (0.25-1.88)	0.76 (0.27-2.09)
Sensitivity analyses								
Excluding stage 0 breast cancer								
Cancer-free	12/4071	1.00 (ref)	1.00 (ref)	1.00 (ref)	21/4494	1.00 (ref)	1.00 (ref)	1.00 (ref)
Survivor	16/1135	4.32 (2.01-9.28)	4.26 (1.93-9.38)	4.35 (1.96-9.65)	4/1318	0.63 (0.22-1.85)	0.65 (0.21-1.95)	0.68 (0.22-2.07)
Excluding stage IV breast cancer								
Cancer-free	12/4071	1.00 (ref)	1.00 (ref)	1.00 (ref)	21/4494	1.00 (ref)	1.00 (ref)	1.00 (ref)
Survivor	18/1370	4.05 (1.92-8.53)	4.02 (1.87-8.62)	4.06 (1.88-8.77)	5/1598	0.66 (0.25-1.75)	0.69 (0.25-1.90)	0.76 (0.27-2.11)
Excluding early bilateral oophorectomy[c]								
Cancer-free	8/3888	1.00 (ref)	1.00 (ref)	1.00 (ref)	21/4242	1.00 (ref)	1.00 (ref)	1.00 (ref)
Survivor	15/1328	5.08 (2.10-12.27)	5.70 (2.34-13.89)	5.67 (2.32-13.87)	5/1528	0.64 (0.24-1.71)	0.65 (0.24-1.79)	0.74 (0.27-2.02)
Excluding pre- to post-menopausal								
Cancer-free	11/2815	1.00 (ref)	1.00 (ref)	1.00 (ref)	12/3091	1.00 (ref)	1.00 (ref)	1.00 (ref)
Survivor	13/975	3.15 (1.37-7.23)	2.74 (1.13-6.63)	2.80 (1.15-6.81)	2/1197	0.41 (0.09-1.87)	0.38 (0.08-1.85)	0.45 (0.09-2.18)

Abbreviations: CVD, cardiovascular disease; MV, multivariable

[a] Model adjusted for age (years), race (white, other), education status (≥4-year college, <4-year college), menopausal status at baseline (premenopausal, postmenopausal), body mass index (kg/m^2), physical activity (MET-h/week), smoking status (never, ever), alcohol intake (grams/day) and hormone replacement therapy (never, ever)

[b] Model mutually adjusted for other CVD risk factors: hypertension, high cholesterol, high triglycerides, and diabetes

[c] Model for incident high triglycerides that mutually adjusted for other CVD risk factors does not adjust for diabetes due to no women with prevalent diabetes

Table 3-3. Hazard ratios and 95% confidence intervals for incident cardiovascular disease risk factors in breast cancer survivors stratified by breast cancer characteristics compared to cancer-free women

	Hypertension (N=777)		**High cholesterol (N=675)**		**High triglycerides (N=828)**	
	Events/ person-years	MV-adjusted HR[a] (95% CI)	Events/ person-years	MV-adjusted HR[a] (95% CI)	Events/ person-years	MV-adjusted HR[a] (95% CI)
Age at diagnosis						
Cancer-free	45/3696	1.00 (ref)	50/3177	1.00 (ref)	12/4071	1.00 (ref)
≤50 years	13/756	2.04 (1.04-4.00)	9/690	0.87 (0.41-1.83)	9/799	4.37 (1.66-11.53)
>50 years	7/509	0.76 (0.33-1.77)	12/387	1.19 (0.59-2.37)	9/588	3.58 (1.34-9.56)
Menopausal status at diagnosis						
Cancer-free	45/3696	1.00 (ref)	50/3177	1.00 (ref)	12/4071	1.00 (ref)
Premenopausal at diagnosis	15/852	1.72 (0.92-3.20)	11/759	0.79 (0.40-1.55)	10/892	3.51 (1.42-8.71)
Postmenopausal at diagnosis	5/413	0.70 (0.26-1.88)	10/319	1.30 (0.60-2.81)	8/495	3.20 (1.12-9.17)
ER-status[b]						
Cancer-free	45/3696	1.00 (ref)	50/3177	1.00 (ref)	12/4071	1.00 (ref)
ER-negative	0/232	--	4/178	1.45 (0.50-4.22)	6/214	7.61 (2.50-23.17)
ER-positive	15/778	1.52 (0.83-2.80)	14/692	0.98 (0.53-1.81)	10/893	3.29 (1.34-8.07)

Abbreviations: CVD, cardiovascular disease; ER, estrogen-receptor; MV, multivariable

[a] Adjusted for age (years), race (white, other), education status (≥4-year college, <4-year college), menopausal status at baseline (premenopausal, postmenopausal), body mass index (kg/m^2), physical activity (MET-h/week), smoking status (never, ever), alcohol intake (grams/day) and hormone replacement therapy (never, ever)

[b] ER-status is among invasive breast cancer only

Table 3-4. Hazard ratios and 95% confidence intervals for incident cardiovascular disease risk factors among breast cancer survivors compared to cancer-free women stratified by baseline body mass index categories

BMI categories	**Hypertension (N=777)**			**High cholesterol (N=675)**			**High triglycerides (N=828)**		
	Events/ person-time	MV-adjusted HR[a] (95% CI)	p-value[b]	Events/ person-time	MV-adjusted HR[a] (95% CI)	p-value[b]	Events/ person-time	MV-adjusted HR[a] (95% CI)	p-value[b]
BMI <25 kg/m^2									
Cancer-free	12/2187	1.00 (ref)		23/1910	1.00 (ref)		7/2232	1.00 (ref)	
Survivors	5/804	0.91 (0.30-2.75)		9/667	0.80 (0.36-1.81)		7/849	2.20 (0.69-7.04)	
BMI ≥25 kg/m^2			0.64			0.71			0.10
Cancer-free	33/1510	1.00 (ref)		27/1266	1.00 (ref)		5/1838	1.00 (ref)	
Survivors	15/461	1.54 (0.81-2.92)		12/411	1.18 (0.58-2.39)		11/538	7.88 (2.61-23.79)	

Abbreviations: HR, hazard ratios; CI, confidence interval; MV, multivariable; BMI, body mass index

[a]Model adjusted for age (years), race (white, other), education status (≥4-year college, <4-year college), menopausal status at baseline (premenopausal, postmenopausal), body mass index (kg/m^2), physical activity (MET-h/week), smoking status (never, ever), alcohol intake (grams/day) and hormone replacement therapy (never, ever)

[b] P value for likelihood ratio test of interaction between breast cancer status and BMI

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Chapter 4.

Evaluation of osteopenia and osteoporosis in younger breast cancer survivors compared to cancer-free women: A prospective study within a familial risk cohort

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Abstract

Background: Osteoporosis has been consistently reported among older breast cancer survivors. However, data is limited on the incidence of osteoporosis and osteopenia, an earlier indicator of bone loss, in breast cancer survivors relative to their cancer-free peers.

Methods: We identified 211 survivors diagnosed with breast cancer ≤5 years prior to baseline and 567 cancer-free women from an ongoing familial risk cohort. Multivariable (MV)-adjusted Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of incident osteopenia and/or osteoporosis based on physician diagnosis.

Results: Mean age at diagnosis was 47 years. During a mean follow-up time of 5.8 years, 66% of breast cancer survivors and 53% of cancer-free women reported having a bone density exam and 112 incident cases of osteopenia/osteoporosis were identified. Overall, breast cancer survivors had a 68% higher risk of osteopenia and osteoporosis compared to cancer-free women (MV-HR=1.68, 95% CI=1.12-2.50). The association was stronger among recent survivors after only 2 years of follow-up (MV-HR=2.74, 95% CI=1.37-5.47). A higher risk of osteopenia and osteoporosis was also observed among the following subgroups; survivors ≤50 years, survivors with ER positive tumors, and survivors treated with aromatase inhibitors (AI) alone or with chemotherapy plus any hormonal therapy when compared to cancer-free women**.**

Conclusion Young breast cancer survivors are at higher risk for osteopenia and osteoporosis compared to cancer-free individuals. Studies are needed to determine effective approaches to minimize bone loss in this population.

Introduction

Osteopenia and osteoporosis, both systemic skeletal conditions associated with varying degrees of bone loss, are prevalent among postmenopausal breast cancer survivors with reports of up to 80% of survivors experiencing bone loss.[1] Osteopenia is diagnosed among individuals with lower than average bone density while osteoporosis is characterized by even lower bone density and architectural deterioration of bone tissue.[2] Untreated bone loss can also lead to subsequent fractures and death.[3] Among breast cancer survivors, cancer-related risk factors for osteopenia and osteoporosis include both treatment and premature menopause.[1,4] The excess risk of osteopenia and osteoporosis among breast cancer survivors relative to their cancer-free peers remains unknown.

Osteopenia and osteoporosis are also common conditions in the general population. Among women aged ≥50 years in the United States, approximately 15.4% have osteoporosis and 51.4% have low bone density.[5] Furthermore, 1 in 2 women will be at risk for an osteoporosis-related fracture during their lifetime.[6] Among cancer-free women, loss in bone density is due to advancing age, menopause induced estrogen deficiency, and other modifiable factors including low body weight, lack of physical activity, excess alcohol consumption, family history of bone fracture, cigarette smoking, low calcium intake, and vitamin D deficiency.[4,7] Loss of bone density in breast cancer survivors could be due to similar risk factors in addition to treatment related effects. By comparing cancer survivors to cancer-free individuals, we are able to differentiate between these risk factors.

Few epidemiologic studies have examined osteopenia and osteoporosis in breast cancer survivors relative to cancer-free women within the same cohort.[8-10] One prior study reported significantly

lower levels of bone mineral density,[8] the gold standard for assessing bone loss, and two other previous studies observed an increased risk of osteopenia and osteoporosis[9,10] compared to cancer-free women. These studies were primarily conducted among older and long-term breast cancer survivors and did not differentiate based on tumor subtypes and detailed treatment regimens. One reason for the paucity of studies among younger breast cancer survivors is likely the challenge of identifying a comparable cancer-free group as young cancer-free women do not routinely undergo assessment of their bone health. Fortunately, we found this not to be the case in women with familial breast cancer risk. In this study, we examined the risk of osteopenia and osteoporosis in young breast cancer survivors compared to cancer-free women in a familial risk cohort known as the Breast and Ovarian Surveillance Service (BOSS) study.

Methods

Study population

The Breast and Ovarian Surveillance Service (BOSS) study is an ongoing prospective cohort study that enrolled women and men with familial risk for breast and/or ovarian cancer.[11] Participants were enrolled from 2005-2013 primarily from the cancer genetics clinic at the John Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland. Eligible participants were aged ≥18 years with either: 1) a family history of breast and/or ovarian cancer, 2) a documented BRCA1/2 mutation, 3) a diagnosis with breast cancer at ≤40 years of age without a family history of breast cancer, or 4) a diagnosis with ovarian cancer at any age without a family history of ovarian cancer. Participants completed a baseline questionnaire to collect information on a variety of demographic, lifestyle, and health factors including detailed information on medical history and breast cancer treatment. Subsequent follow-up questionnaires

have been completed every 3-4 years thereafter (>92% have completed at least 1 follow-up questionnaire). Completion of the second follow-up questionnaire is ongoing.

For the present analysis, women were included if they completed a baseline questionnaire and at least 1 follow-up questionnaire through September 30th, 2017 (n=1,173). Women with a physician diagnosis of osteopenia or osteoporosis at baseline (n=272 total; n=174 with osteopenia only; n=46 osteoporosis only) or bisphosphonate use at baseline (n=5) were excluded. We further excluded women with missing responses for osteopenia or osteoporosis on baseline (n=1) or follow-up questionnaires (n=5). For this analysis, breast cancer survivors were defined as women diagnosed with breast cancer (ductal carcinoma *in* situ [stage 0] or stage I-III breast cancer) within 5 years prior to enrollment. The comparison group was restricted to women with no prior history of cancer at baseline except non-melanoma skin cancer or cervical carcinoma *in situ*. After these exclusions, 778 women (211 breast cancer survivors and 567 cancer-free) became our analytic study population.

Ascertainment of breast cancer and treatment

Cancer diagnoses were self-reported at enrollment and pathology records were reviewed to confirm breast cancer diagnosis (International Classification of Disease-10 code: invasive breast cancer [C50]; ductal carcinoma in situ [D05.1] and lobular carcinoma in situ [D05.0]) as well as stage and hormonal receptor status (estrogen/progesterone receptor and HER2 status). Breast cancer treatment was reported in baseline questionnaires and details were confirmed with medical record review (96% confirmed). Treatment information included surgery (none, lumpectomy, mastectomy), and adjuvant therapy (chemotherapy, radiation, and hormonal therapy). Detailed information on type of chemotherapy and hormonal therapy was also collected. We classified cancer treatment into mutually exclusive categories of surgery only, hormonal therapy alone,

chemotherapy alone, and chemotherapy plus hormonal therapy. Hormonal therapy was further classified as tamoxifen or aromatase inhibitor use.

Ascertainment of osteopenia and osteoporosis

Osteopenia and osteoporosis diagnoses were ascertained in baseline and follow-up questionnaires. In each questionnaire, participants were asked to indicate whether they had received a physician's diagnosis and the year of diagnosis for osteopenia and osteoporosis. Incident cases of osteopenia and osteoporosis were identified on follow-up questionnaires. Our outcome of interest was a composite outcome that included incident osteopenia and/or osteoporosis. Participants also reported whether they ever had a bone density exam and the year of exam on both baseline and follow-up questionnaires.

Ascertainment of covariates

Information on covariates (age, race, education level, menopausal status, age at menopause, oophorectomy at a young age, body mass index [BMI], physical activity based on metabolic equivalents of task [METs] per week, alcohol intake, smoking status, hormonal replacement therapy [HRT] use, current bisphosphonate use, history of screening [mammography, pap smear], vitamin D supplement use, and calcium supplement use) were available from the baseline questionnaire. Bilateral oophorectomy at a young age was defined as both ovaries removed prior to age 45 years and based on self-report. We calculated age at bilateral oophorectomy from the date that the second ovary was removed. Year of medical procedures and screening exams, including mammograms, pap smears, sigmoidoscopy, and colonoscopy, were also reported on both baseline and follow-up questionnaires.

Statistical analysis

Baseline characteristics of breast cancer survivors and cancer-free women were compared with frequency distributions for categorical variables and means (SDs) for continuous variables. We used Cox proportional hazard models with age as the time scale to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Women contributed person-time from the completion date of the baseline questionnaire to the date of osteopenia or osteoporosis diagnosis or until end of last follow-up through September 30th, 2017, whichever occurred first. The proportional hazards assumption was assessed with log-log survival plots and Schoenfeld residuals; neither method indicated that the assumption of proportional hazards by breast cancer status was violated. Confounders were identified a priori as variables that may be associated with both breast cancer incidence and osteopenia/osteoporosis. Multivariable models were adjusted for menopausal status (premenopausal, postmenopausal), hormone replacement therapy (ever, never), body mass index (BMI) (kg/m^2), bilateral oophorectomy at age <45 years (yes, no), physical activity (MET-h/week), smoking status (ever, never) and alcohol use (g/day). To account for a small percent of missing (< 1% missing), we imputed missing data with the most common category for categorical covariates and the median value for continuous covariates among cancer-free women. Our primary models were conducted among women diagnosed with stage 0-III breast cancer relative to cancer-free women. In addition, we also conducted all analyses with breast cancer status restricted to invasive cancer (stage I-III) relative to cancer-free women.

We conducted several sensitivity analyses. First, we restricted our analytic population to women who reported having a prior bone density exam at baseline to reduce the potential inclusion of undiagnosed prevalent cases. Second, we restricted our analytic population to women who reported a bone density exam during follow-up to reduce the potential misclassification of incident cases. Third, we conducted an analysis among women with no change in menopause

over follow-up to determine if menopause might drive the development of bone loss. Finally, we ran several models that excluded women who reported a bilateral oophorectomy at age <45 years, vitamin D use at baseline, or calcium use at baseline.

We also examined the risk of osteopenia and osteoporosis in women with breast cancer stratified by age at diagnosis, menopausal status at diagnosis, estrogen-receptor (ER) tumor status, and breast cancer treatment relative to cancer-free women. For models that stratified breast cancer survivors by ER-status, survivors were restricted to invasive breast cancer since ER status was not routinely measured in women with a stage 0 diagnosis. We additionally conducted several exploratory analyses by family history of breast cancer (no family history, first degree relative only, first and second degree relative) and BRCA 1/2 carrier status among a subgroup of women with genetic testing. We were unable to conduct analyses by HER2 status or triple negative breast cancer due to small numbers.

Finally, to examine whether risk of osteopenia and osteoporosis varied by time since diagnosis, we used time since enrollment as the time metric and restricted breast cancer survivors to women diagnosed within 1 year prior to enrollment. Models were then stratified by follow-up time (≤2 years and >2 years) and heterogeneity was tested using the likelihood ratio test.

Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 14.0 (Stata Corp LP, College Station, TX, USA). All statistical tests were two-side and P values ≤0.05 were considered statistically significant.

Results

Table 4-1 describes age and age-adjusted baseline characteristics of 778 women by breast cancer status (211 breast cancer survivors and 567 cancer-free women). Compared to cancer-free women, breast cancer survivors were more likely to be slightly older, postmenopausal, and current vitamin D users and less likely to have a bilateral oophorectomy at a young age and a family history of breast cancer. Both groups were predominately white and highly educated (≥4-years of college). Among breast cancer survivors, the mean time from diagnosis to enrollment was 1.4 years and the mean age at diagnosis was 47 years. Over 80% of breast cancer survivors were diagnosed with a first invasive breast cancer and 76% had ER-positive breast tumors. In addition, all breast cancer survivors received surgery prior to adjuvant therapy, 65% of breast cancer survivors received any hormonal therapy (67% tamoxifen, 41% aromatase inhibitors) and 50% received any chemotherapy.

During an average of 5.8 years of follow-up, there were 112 incident cases of osteopenia and/or osteoporosis (75% osteopenia only). The incidence rate for osteopenia and osteoporosis was 44 cases/1000 person-years among breast cancer survivors compared to 19 cases/1,000 person-years in cancer-free women. Overall, breast cancer survivors had a 68% higher risk of osteopenia and osteoporosis compared to cancer-free women (MV-HR=1.68, 95% CI=1.12-2.50) (Table 4-2). The magnitude of risk was even stronger among invasive breast cancer survivors compared to cancer-free women (MV-HR=1.90; 95% CI=1.24-2.90). Our results were similar to our primary analysis when we restricted our analytic population to women who reported having a bone density exam prior to baseline and during follow-up (MV-HR=1.90, 95% CI=1.08-3.34; MV-HR=1.72, 95% CI=1.14-2.58, respectively). Results were also similar when we excluded women who had premature menopause secondary to a bilateral oophorectomy at age <45 years (MV-HR=1.63, 95% CI=1.08-2.46) and only slightly attenuated when we restricted our analysis to women with no change in menopause status during follow-up (MV-HR=1.57, 95% CI=0.93-2.63). Finally, results did not change when we restricted our analytic sample to women without

vitamin D use at baseline (MV-HR=1.68, 95% CI=1.08-2.61) and became slightly attenuated among women without calcium use at baseline (MV- HR= 1.59, 95% CI=0.95-2.68).

Next, we examined the risk of osteopenia and osteoporosis in breast cancer survivors stratified by age at diagnosis, menopausal status at diagnosis, and ER-status compared to cancer-free women (Table 4-3). Breast cancer survivors diagnosed at age ≤50 years had an almost 2-fold increased risk of osteopenia and osteoporosis compared to cancer-free women (HR=1.98, 95% CI=1.21-3.24). Surprisingly, the association was not significant in older women. In addition, breast cancer survivors who were premenopausal at diagnosis had increased risk of osteopenia and osteoporosis relative to their cancer-free peers (MV-HR=1.76, 95% CI=1.09-2.84) and this risk was similar, but attenuated, among women who were postmenopausal at diagnosis (MV-HR=1.58, 95% CI=0.86-2.89). Finally, women with ER-positive tumors had an over 2-fold increased risk of osteopenia and osteoporosis compared to cancer-free women (MV-HR=2.10; 95%=1.34-3.29). Although women with ER-negative tumors had a modest increased risk of osteopenia and osteoporosis relative to their cancer-free peers, the association was not statistically significant (MV-HR=1.26; 95% CI=0.54-2.94). In exploratory analyses, results were attenuated but did not differ by family history of breast cancer and BRCA 1/2 carrier status (data not shown).

We then evaluated risk of osteopenia and osteoporosis in breast cancer survivors stratified by breast cancer treatment compared to cancer-free women (Figure 4-1). Breast cancer survivors treated with chemotherapy plus hormonal therapy had over 2-fold increased risk of incident osteopenia and osteoporosis compared to cancer-free women (MV-HR=2.70; 95% CI=1.56-4.68). No significant association was observed for breast cancer survivors treated with surgery, chemotherapy, or hormonal therapy alone compared to cancer-free women. Breast cancer survivors treated with aromatase inhibitors alone and combined chemotherapy plus aromatase inhibitors had over 2- and 3-fold increased risk of osteopenia and osteoporosis compared to

cancer-free women (MV-HR=2.72, 95% CI=1.31-5.65; MV-HR=3.83, 95% CI=1.87-7.83, respectively). In addition, breast cancer survivors treated with chemotherapy plus tamoxifen had an over 2-fold increased risk compared to cancer-free women (MV-HR=2.48, 95% CI=1.16-5.30).

Finally, breast cancer survivors diagnosed within 1 year prior to enrollment had an over 2-fold increased risk of osteopenia and osteoporosis compared to their cancer-free peers within the first 2 years of follow-up (MV-HR=2.74, 95% CI=1.37-5.47) and a non-significant 85% increased risk of osteopenia and osteoporosis after 2-years of follow-up (MV-HR=1.85, 95% CI=0.98-3.51), although p-values for heterogeneity were not significant (p=0.44) (Table 4-4).

Discussion

To our knowledge this is the first study to prospectively assess risk of osteopenia and osteoporosis in young and recently diagnosed breast cancer survivors compared to their cancer-free peers in a familial high risk cohort. In this study, the risk of osteopenia and osteoporosis was almost two-fold higher in breast cancer survivors compared to cancer-free women over an average of 5.8 years of follow-up. Breast cancer survivors who were aged 50 years or younger at diagnosis, had ER+ tumors, received AIs alone, or combined chemotherapy with AI or tamoxifen hormone therapy had a higher risk of osteopenia and osteoporosis compared to cancer-free women. This is after accounting for age, menopause and other risk factors for bone loss.

The majority of studies have used a case-only design to examine bone health in breast cancer survivors.[12-20] Several studies have found a higher risk of fracture in women diagnosed with breast cancer compared to cancer-free women,[21-23] however results have been inconsistent.[24,25]

Even fewer epidemiologic studies have assessed osteopenia and osteoporosis risk in women with breast cancer compared to their cancer-free peers within the same cohort.[8-10] Furthermore, these studies have included primarily older and long-term survivors. The first of these studies was conducted among the Women's Health Initiative Observational Study (WHI-OS). This study compared the prevalence of osteoporosis and the rate of bone loss in post-menopausal breast cancer survivors compared to cancer-free women.[8] Although the investigators found that breast cancer survivors had a higher prevalence of low bone density and osteoporosis at baseline, they did not have an increased rate of bone loss compared to cancer-free women over follow-up. A limitation of this study was that breast cancer survivors were identified from prevalent cases at study enrollment and the time from breast cancer diagnosis to study enrollment was not reported. It is possible that the rate of bone loss may have been assessed too distal to cancer diagnosis or treatment cessation, particularly if substantial bone loss occurs shortly after diagnosis or treatment.

The second study was a retrospective registry study in the Cancer Genetics Network (CGN) conducted to assess early and late effects of cancer treatment.[9] In this study, the authors assessed osteopenia and osteoporosis risk based on self-report in women with and without invasive breast cancer and found a significant positive association for both outcomes (HR: 2.1, 95% CI: 1.8-2.4 for osteopenia; HR: 1.5, 95% CI: 1.2-1.9 for osteoporosis). Although this study included younger women with familial cancer risk, breast cancer survivors were identified from 1990 to 2009 and history of bone health was collected retrospectively in 2009. Among these breast cancer survivors, over 70% were diagnosed ≥10 years prior to the assessment of self-reported bone health in 2009 and thus susceptible to substantial recall bias.

The third study was conducted among the UK general practice research database (GPRD) to examine long-term health outcomes among older cancer survivors and cancer-free individuals

(overall mean age [SD]=66.9 years [12.3 years]).[10] The authors assessed osteoporosis risk, but not osteopenia, based on medical records among breast cancer survivors and found that survivors had a 26% higher risk of osteoporosis compared to cancer-free women (HR: 1.26, 95% CI: 1.13-1.40). No prior study has assessed bone loss by tumor subtype or incorporated detailed information on cancer treatment and bone scan history. In addition, only one previous study assessed osteopenia risk,[9] an earlier indication of bone loss, which is also associated with a high fracture risk.

The most common cause of bone loss in women is menopause and aging. Aging is associated with greater bone resorption and less bone formation while menopause induces accelerated bone loss due to lowering levels of endogenous estrogen.[26] Therefore, a cancer-free comparison of similar age and menopausal status is important when assessing bone loss. Given that we still observed significantly higher bone loss in breast cancer survivors relative to their cancer-free peers after accounting for age and and menopause, it is likely that additional bone loss is due to the effect of treatment on bone formation.

We observed the highest risk of osteopenia and osteoporosis among breast cancer survivors treated with AIs alone and chemotherapy plus AIs. These findings are in agreement with the underlying biology of AIs[27] as well as case only studies in survivors [16-20] and high-risk women in chemoprevention trials.[28,29] AIs, prescribed to post-menopausal women with ER-positive tumors, block the aromatase enzyme resulting in a hypoestrogen state which is associated with bone loss.[27] We found no association among women with tamoxifen use alone, a group that was primarily premenopausal at baseline (mean age at baseline=46 years; 76% premenopausal at baseline). However, we did observe an almost 2-fold increased risk of osteopenia and osteoporosis among women with chemotherapy plus tamoxifen use (mean age at baseline=43; 50% premenopausal at baseline). Although tamoxifen, a selective estrogen receptor modulator, is

generally thought to be protective against bone loss in postmenopausal women,[30] reports suggest that it may cause bone loss among premenopausal women.[13,31] It is hypothesized that chemotherapy may also cause bone loss due to treament induced premature menopause in premenopausal women[32] and may also have direct toxic effects on bone formation cells.[27] In addition, medications commonly presribed along with chemotherapy (e.g., steroids) have also been associated with bone loss.[33] Therefore, it is biologically plausible that chemotherapy plus hormonal therapy, including tamoxifen, might have a joint deleterious effect on bone health.

The strengths of this study include the prospective study design, direct comparison to cancer-free women from the same cohort, and detailed information on cancer treatment. There are also several limitations to our prospective analysis. First, our sample size may have limited our power to detect small to moderate associations. Second, osteopenia and osteporosis incidence was ascertained based on self-reported physican diagnosis and may be susceptible to misclassification. However 96% of women who reported a diagnosis of osteopenia or osteopororisis also reported receiving a bone scan and analyses restricted to women who reported having a bone scan during follow-up were similar. Third, breast cancer survivors may have had increased surveillance for bone health and therefore, screening might not have been comparable to cancer-free women. It is possible that osteopenia or osteoporosis may be underdiagnosed in cancer-free women. However, overall health screening history was similar at baseline among breast cancer survivors vs. cancer-free women (e.g., 99.1% of breast cancer survivors vs 98.8% cancer-free women ever had a pap-smear; 97.8% of breast cancer survivors vs. 99.5% of cancer-free women ever had a mammogram among women aged ≥ 50 years). In addition, compared to cancer-free women, breast cancer survivors were only slightly more likely to have had a bone density exam at baseline (43% vs. 29%; 60% vs. 51% among women aged ≥45 years) and follow-up (66% vs 53%). To further reduce the possibility of undetected prevalent cases, we restricted our analysis to women with bone density exams prior to baseline and results were similar (MV-HR=1.90, 95% CI=1.08-3.34).

Finally, our results may not be generalizable to other populations since our study population was predominately white and highly educated women at high risk for breast cancer. However, we believe that the underlying biology is likely similar across ethnicities. Future studies in more diverse populations are needed. The homogeniety of our study population however improves the internal validity of this study as it reduces the influence of potential unmeasured factors.

In summary, our results demonstrate that incident osteoporosis and osteopenia is significantly higher in young breast cancer survivors with familial risk compared to cancer-free women and risk varies by cancer subtype and breast cancer treatment. These findings provide support for a baseline evaluation of bone density and fracture risk assessment close to breast cancer diagnosis, particularly among young breast cancer survivors being treated with combined chemotherapy and hormone therapy, so that prevention strategies and appropriate monitoring can be implemented. Future studies are needed to address the frequency of monitoring in breast cancer survivors by specific age and treatment groups.

Table 4-1. Age- and age-adjusted baseline characteristics of cancer-free women and breast cancer survivors in the BOSS cohort study

Characteristic	Cancer-free (n=567)	Survivors[a] (n=211)	p-value
Age[b], mean years (SD)	44.7 (11.3)	48.1 (10.3)	<0.001
White, %	88.7	83.3	0.02
Education, ≥4-year college, %	77.6	77.4	0.72
Postmenopausal, %	27.4	51.6	<0.001
Age at menopause[c], mean years (SD)	49.6 (4.9)	48.8 (3.4)	0.86
Bilateral oophorectomy at age < 45 years[d], %	49.0	34.3	0.02
BMI, mean kg/m^2 (SD)	26.2 (5.1)	25.9 (3.1)	0.29
Physical activity, mean MET-h/week[e] (SD)	29.4 (27.9)	26.0 (15.5)	0.29
Alcohol intake, mean g/day (SD)	5.7 (7.5)	5.7 (4.8)	0.99
Smoking status, %			
Never	58.8	52.5	0.55
Former	36.7	44.8	
Current	4.2	2.7	
Missing	0.3	0.0	
Hormone replacement therapy ever use, %	15.1	14.5	0.04
Ever mammogram[f], %	99.5	97.8	0.63
Ever pap smear, %	98.6	99.1	0.15
Current vitamin D supplement use, %	7.8	20.8	<0.001
Current calcium supplement use, %	25.5	28.1	0.97
Bone density screening, %	28.9	43.0	0.02
Bone density screening in women aged ≥45 years, %	51.2	60.0	0.08
Ever broken bone, %	6.4	6.8	0.84
Family history of breast cancer, %			
No family history of breast cancer	14.7	38.9	<0.001
First degree relative only	64.8	50.7	
First and second degree relative	17.0	9.0	
Missing	3.5	1.4	
BRCA 1/2 status[g], %			
Negative	69.7	73.9	0.33
Positive	27.3	19.4	
Variants of uncertain significance	2.9	6.7	
Age at diagnosis, mean years (SD)	--	46.8 (10.2)	--
Time from diagnosis to baseline, mean years (SD)	--	1.4 (1.3)	--
Invasive breast cancer (stage I-III), %	--	82.5	--
Estrogen receptor status[h], %	--		--
Positive	--	75.9	--
Negative	--	23.6	--
Missing/untested	--	<1	--
HER2 status[h], %	--		--
Positive	--	14.4	--
Negative	--	81.6	--

Missing/untested	--	3.5	--
Triple negative status[h], %	--	19.0	--
Breast cancer treatment[i,j], %	--		--
Surgery	--	100.0	--
Chemotherapy	--	49.8	--
Hormonal therapy, any	--	65.4	--
Hormonal therapy [k], by type	--		--
Tamoxifen	--	67.4	--
Aromatase inhibitor	--	41.3	--

Abbreviations: HER2, human epidermal growth factor receptor 2

Values are means(SD) or percentages and are standardized to the age distribution of the study population

[a] Women were diagnosed with stage 0-III breast cancer ≤5 years prior to baseline

[b] Value is not age-adjusted

[c] Among post-menopausal women

[d] Among women who had both ovaries removed (n=86)

[e] Metabolic equivalents from recreational and occupational activity

[f] Among women aged ≥50 years

[g] Among women tested for BRCA status (n=414)

[h] Among invasive cases only (n=174)

[i] Treatment groups are not mutually exclusive

[j] Chemotherapy and hormonal therapy are adjuvant

[k] 7% breast cancer survivors received both tamoxifen and aromatase inhibitors (n=15)

Table 4-2. Hazard ratios and 95% confidence intervals for incident osteopenia and osteoporosis among breast cancer survivors compared to cancer-free women

	Stage 0-III breast cancer survivors			**Stage I-III breast cancer survivors**		
	Events/ person-years	Age-adjusted HR (95% CI)	MV-adjusted HR[a] (95% CI)	Events/ person-years	Age-adjusted HR (95% CI)	MV-adjusted HR[a] (95% CI)
Overall						
Cancer-free	67/3509	1.00 (ref)	1.00 (ref)	67/3509	1.00 (ref)	1.00 (ref)
Breast cancer survivors	45/1026	2.01 (1.38-2.94)	1.68 (1.12-2.50)	39/819	2.18 (1.46-3.24)	1.90 (1.24-2.90)
Excluding women without bone density exams prior to baseline						
Cancer-free	27/1023	1.00 (ref)	1.00 (ref)	27/1023	1.00 (ref)	1.00 (ref)
Breast cancer survivors	27/497	1.96 (1.15-3.36)	1.90 (1.08-3.34)	23/400	2.10 (1.20-3.67)	2.13 (1.17-3.90)
Excluding women without bone density exams during follow-up						
Cancer-free	63/1890	1.00 (ref)	1.00 (ref)	63/1890	1.00 (ref)	1.00 (ref)
Breast cancer survivors	45/703	1.89 (1.29-2.78)	1.72 (1.14-2.58)	39/577	1.98 (1.33-2.97)	1.91 (1.24-2.93)
Excluding early bilateral oophorectomy prior to baseline[b]						
Cancer-free	64/3347	1.00 (ref)	1.00 (ref)	64/3347	1.00 (ref)	1.00 (ref)
Breast cancer survivors	42/957	1.93 (1.30-2.85)	1.63 (1.08-2.46)	36/755	2.08 (1.38-3.14)	1.85 (1.19-2.86)
Excluding pre- to post-menopausal during follow-up						
Cancer-free	34/2308	1.00 (ref)	1.00 (ref)	34/2308	1.00 (ref)	1.00 (ref)
Breast cancer survivors	32/745	2.18 (1.34-3.55)	1.57 (0.93-2.63)	28/595	2.38 (1.44-3.95)	1.71 (0.99-2.94)
Excluding current vitamin D users[c]						
Cancer-free	60/3263	1.00 (ref)	1.00 (ref)	60/3263	1.00 (ref)	1.00 (ref)
Breast cancer survivors	36/820	2.03 (1.34-3.08)	1.68 (1.08-2.61)	31/661	2.20 (1.42-3.40)	1.93 (1.21-3.09)
Excluding current calcium users[c]						
Cancer-free	40/2637	1.00 (ref)	1.00 (ref)	40/2637	1.00 (ref)	1.00 (ref)
Breast cancer survivors	28/743	2.14 (1.32-3.48)	1.59 (0.95-2.68)	24/625	2.24 (1.35-3.74)	1.78 (1.03-3.08)

Abbreviations: HR, hazard ratios; CI, confidence interval; MV, multivariable

[a]Adjusted for age (years), menopausal status (premenopausal, postmenopausal), bilateral oophorectomy at age <45 years (yes, no), body mass index (kg/m^2), physical activity (MET-h/week), smoking status (never, ever), alcohol intake (grams/day) and hormone replacement therapy (never, ever)

[b] Both ovaries removed prior to age 45 years

[c] Vitamin D and calcium supplement use was ascertained at baseline

Table 4-3. Hazard ratios and 95% confidence intervals for incident osteopenia and osteoporosis among breast cancer survivors stratified by breast cancer characteristics compared to cancer-free women

	Stage 0-III breast cancer survivors			**Stage I-III breast cancer survivors**		
	Events/ person-years	Age-adjusted HR (95% CI)	MV-adjusted HR[a] (95% CI)	Events/ person-years	Age-adjusted HR (95% CI)	MV-adjusted HR[a] (95% CI)
Age at diagnosis						
Cancer-free	67/3509	1.00 (ref)	1.00 (ref)	67/3509	1.00 (ref)	1.00 (ref)
≤50 years	27/651	2.34 (1.46-3.75)	1.98 (1.21-3.24)	24/510	2.67 (1.63-4.36)	2.34 (1.39-3.95)
>50 years	18/375	1.64 (0.93-2.88)	1.34 (0.75-2.40)	15/309	1.64 (0.90-2.99)	1.45 (0.78-2.67)
Menopause status at diagnosis						
Cancer-free	67/3509	1.00 (ref)	1.00 (ref)	67/3509	1.00 (ref)	1.00 (ref)
Premenopausal at diagnosis	27/728	1.97 (1.24-3.12)	1.76 (1.09-2.84)	24/579	2.22 (1.37-3.59)	2.11 (1.27-3.52)
Postmenopausal at diagnosis	18/298	2.05 (1.15-3.64)	1.58 (0.86-2.89)	15/240	2.13 (1.15-3.92)	1.70 (0.90-3.23)
ER-status						
Cancer-free	--	--	--	67/3509	1.00 (ref)	1.00 (ref)
ER-negative	--	--	--	7/200	1.68 (0.76-3.72)	1.26 (0.54-2.94)
ER-positive	--	--	--	32/611	2.32 (1.52-3.55)	2.10 (1.34-3.29)

Abbreviations: HR, hazard ratios; CI, confidence interval; MV, multivariable; ER, estrogen-receptor

[a]Adjusted for age (years), menopausal status (premenopausal, postmenopausal), bilateral oophorectomy at age <45 years (yes, no), body mass index (kg/m^2), physical activity (MET-h/week), smoking status (never, ever), alcohol intake (grams/day) and hormone replacement therapy (never, ever)

Table 4-4. Hazard ratios and 95% confidence intervals for incident osteopenia and osteoporosis among recent breast cancer survivors compared to cancer-free women stratified by follow-up time

	Stage 0-III breast cancer survivors[a]					**Stage I-III breast cancer survivors[a]**				
	Events/ person-years	Age-adjusted HR (95% CI)	p[b]	MV-adjusted HR[c] (95% CI)	p[b]	Events/ person-years	Age-adjusted HR (95% CI)	p[b]	MV-adjusted HR[c] (95% CI)	p[b]
Overall										
Cancer-free	67/3497	1.00 (ref)	--	1.00 (ref)	--	67/3497	1.00 (ref)	--	1.00 (ref)	--
Breast cancer survivors	27/475	2.49 (1.58-3.91)		2.17 (1.37-3.46)		22/385	2.47 (1.51-4.03)		2.18 (1.32-3.59)	
0-2 years										
Cancer-free	22/1126	1.00 (ref)		1.00 (ref)		22/1126	1.00 (ref)		1.00 (ref)	
Breast cancer survivors	14/214	3.15 (1.61-6.17)		2.74 (1.37-5.47)		12/182	3.17 (1.56-6.41)		2.76 (1.34-5.70)	
3+ years			0.42		0.44			0.41		0.44
Cancer-free	45/2371	1.00 (ref)		1.00 (ref)		45/2371	1.00 (ref)		1.00 (ref)	
Breast cancer survivors	13/261	2.07 (1.11-3.85)		1.85 (0.98-3.51)		10/203	1.99 (1.00-3.99)		1.80 (0.89-3.66)	

Abbreviations: HR, hazard ratios; CI, confidence interval; MV, multivariable

[a] Breast cancer survivors were restricted to women diagnosed within 1 year prior to enrollment

[b] P value for likelihood ratio test of interaction between breast cancer status and time

[c] Adjusted for age (years), menopausal status (premenopausal, postmenopausal), bilateral oophorectomy at age <45 years (yes, no), body mass index (kg/m^2), physical activity (MET-h/week), smoking status (never, ever), alcohol intake (grams/day) and hormone replacement therapy (never, ever)

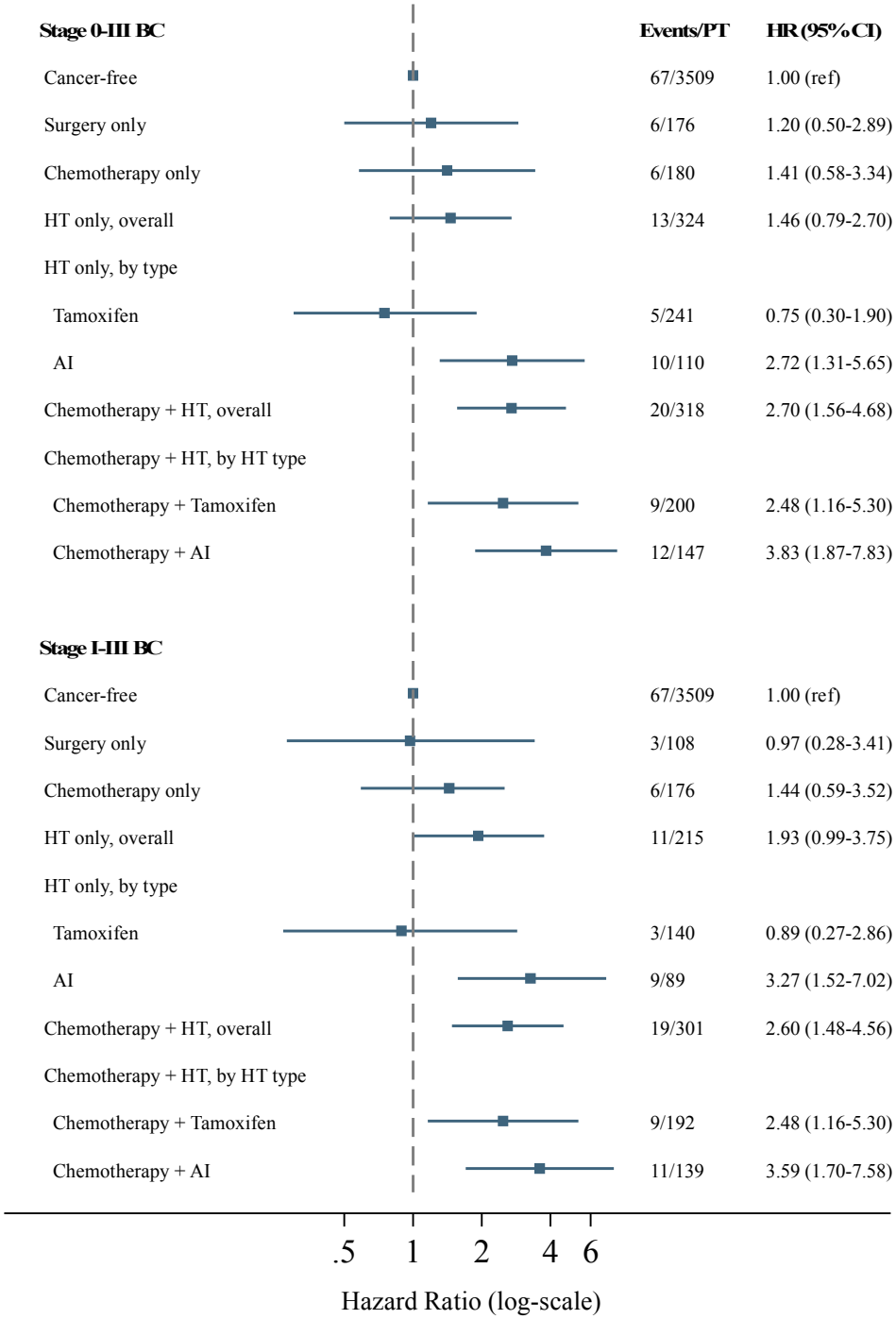

Figure 4-1. Multivariable-adjusted hazard ratios and 95% confidence intervals for incident osteopenia and osteoporosis among breast cancer survivors stratified by type of treatment compared to cancer-free women

Abbreviations: BC, breast cancer; PT, person time in years; HR, hazard ratio; CI, confidence interval; HT, hormone therapy; AI, aromatase inhibitor

Models are adjusted for age (years), menopausal status (premenopausal, postmenopausal), bilateral oophorectomy at age <45 years (yes, no), body mass index (kg/m^2), physical activity (MET-h/week), smoking status (never, ever), alcohol intake (grams/day) and hormone replacement therapy (never, ever)

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Chapter 5. Conclusions

Summary of findings

There is an increasing population of over 3.5 million breast cancer survivors in the United States and many of these women will become long-term survivors with 5-year survival rates now exceeding 90%.[1,2] The overarching goal of this dissertation was to examine the impact of breast cancer and treatment on several adverse outcomes by utilizing a cancer-free comparison from the same cohort and controlling for the effects of aging, menopause, and lifestyle factors. Although bone loss and cardiovascular disease have been reported in breast cancer survivors, the excess risk of these outcomes relative to cancer-free women remains unclear. This dissertation examined the association between bone loss, CVD risk factors, and all-cause and CVD-related mortality in breast cancer survivors compared to cancer-free women. Determining whether breast cancer survivors have a higher risk of these adverse outcomes compared to cancer-free women helps inform the need for tailored treatment and prevention strategies to continue to improve the long-term prognosis after breast cancer.

Chapter 2: All-cause and CVD-related mortality in women with breast cancer

In chapter 2, we examined the risk of all-cause and CVD-related mortality in breast cancer survivors compared to cancer free women in CLUE II, a community-based cohort with over 20-years of follow-up. We further examined this association by breast cancer prognostic factors and time since diagnosis. Overall, we observed a 79% higher risk of all-cause mortality in breast cancer survivors compared to cancer-free women and this increased risk remained 15 years after diagnosis even among women with stage I and ER-positive tumors. These findings highlight the

need to further identify ways to reduce the risk of long-term all-cause mortality among breast cancer survivors.

We also found that risk of all-cause mortality was higher regardless of age at diagnosis. However, risk of all-cause mortality remained steady over time among women diagnosed at age <70 years while this risk increased over time among women diagnosed at age ≥70 years. After 15 years, risk of all-cause mortality was almost 3-fold higher among women diagnosed at age ≥70 years compared to women of similar age without breast cancer. These findings suggest that the risk of dying from any cause differs over time by age at diagnosis, and therefore supports more personalized interventions, particularly among older survivors, to carefully balance the risks and benefits of treatment.

We also observed that breast cancer survivors may have a higher risk of CVD-mortality compared to cancer-free women, and this increased risk begins to manifest several years after diagnosis, particularly among women diagnosed at age ≥70 years and women with ER-positive tumors. These findings suggest a need for early identification of CVD risk among breast cancer survivors shortly after diagnosis. Furthermore, interventions to reduce CVD mortality may be warranted for elderly and ER-positive breast cancer survivors.

Chapter 3: Incident CVD risk factors in women with breast cancer

In chapter 3, we examined whether breast cancer survivors had an increased risk of incident CVD risk factors relative to their cancer-free peers in BOSS, a cohort of women with familial risk for breast cancer. For this study, we focused on potentially modifiable risk factors that develop shortly after diagnosis since we hypothesized that this could be a crucial point of intervention to reduce CVD burden. We found that breast cancer survivors had an almost 4-fold increased risk of

developing high triglycerides relative to their cancer-free peers, and risk of high triglycerides may be even higher among overweight/obese survivors. Finally, we found that women diagnosed at age ≤50 years may have an over 2-fold higher risk of hypertension compared to cancer-free women. Overall, these results suggest that early monitoring of CVD risk factors may be warranted. If additional studies confirm our results, clinicians should monitor triglyceride levels among all breast cancer survivors, particularly among overweight/obese survivors, and blood pressure among breast cancer survivors diagnosed at age ≤50 years.

Chapter 4: Bone loss in women with breast cancer

In chapter 4, we assessed the risk of osteopenia, an early indicator for bone loss, and osteoporosis in breast cancer survivors compared to cancer-free women in the BOSS cohort. In this study, we observed that young breast cancer survivors had an over 2-fold increased risk of osteopenia and osteoporosis relative to their cancer free peers even after accounting for age and menopause, which are strong confounders. This suggests that the underlying etiology of excess bone loss in breast cancer survivors is likely treatment related. We further observed that women diagnosed at age ≤50 years, women with ER-positive tumors, and those treated with AIs or combined chemotherapy plus AIs or tamoxifen had a greater risk of osteopenia and osteoporosis compared to cancer-free women. These findings emphasize the importance of implementing a baseline evaluation of bone density close to breast cancer diagnosis, particularly among young survivors being treated with chemotherapy and tamoxifen, and subsequent monitoring so that early steps can be taken to prevent bone loss.

Future directions

Our findings suggest several future directions for research. First, there are several specific questions that follow directly from our results on all-cause mortality in breast cancer survivors. These include evaluating the effect of treatment regimes and specific treatment over time on the risk of all-cause and cause-specific mortality to clarify how treatment may be driving our results. To further explain the observed increasing risk over time in older survivors, the impact of prevalent and incident comorbidities on mortality should also be assessed. Larger prospective studies with breast cancer survivors and cancer-free women will facilitate examining all of these next steps.

Although, we found that CVD-related mortality may manifest several years after diagnosis, particularly among survivors diagnosed at an older age or with ER-positive tumors, subsequent studies with a larger sample size are needed to confirm these findings. Several questions also follow this research. First, identifying specific types of CVD that are most common among these survivors (e.g., ischemic heart disease, hypertensive heart disease, or heart failure) and examining CVD incidence rather than only CVD-related mortality is needed. If confirmed, research on monitoring for early as well as late cardiovascular toxicity in breast cancer survivors is warranted. In addition, further research is needed to understand smaller changes in cardiac function in breast cancer survivors such as the relationship between hormones and diastolic function. Finally, evaluating whether risk of CVD-mortality could be reduced among high-risk groups by intervening on certain modifiable factors, such as weight loss, physical activity, healthy diet, and preventative medications such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, statins, and aspirin, is needed.

Although our investigation of incident CVD risk factors shortly after diagnosis was novel, these findings need to also be confirmed in larger studies. Since we were limited to a small number of cases, we were unable to detect small to moderate associations and unable to confirm our

hypotheses that specific treatments may play a role in the development of high triglycerides in all breast cancer survivors and hypertension among younger breast cancer survivors. Although, we observed an increased risk of incident CVD risk factors shortly after diagnosis, risk of developing these factors over the long-term and whether these risk factors persist over time needs to be evaluated.

Finally, research efforts should be directed to determine more effective approaches to minimize bone loss in young breast cancer survivors. Our findings suggest that monitoring bone loss in young breast cancer survivors close to diagnosis could prevent the development of osteopenia or progression to osteoporosis. However, the optimal frequency of monitoring, particularly by specific age and treatment groups, remains unknown. Importantly, bone loss is preventable with proper interventions, such as lifestyle and pharmacologic interventions, to preserve bone density or treat established osteoporosis (e.g., bisphosphonates or denosumab).[3,4]

Public health significance

This research contributes novel information on incidence and timing of several short- and long-term adverse outcomes due to breast cancer and its treatment. First, medical surveillance among survivors should further emphasize CVD prevention, particularly among older survivors and women with ER-positive tumors. Second, our findings highlight the need for closer monitoring of incident CVD risk factors, particularly high triglycerides among all breast cancer survivors and hypertension among younger survivors, and implementing interventions shortly after diagnosis to reduce CVD burden. Finally, our research highlights the importance of evaluating bone density close to diagnosis and implementing subsequent monitoring to reduce the risk of bone loss among even young breast cancer survivors, particularly among those treated with chemotherapy and

tamoxifen. Importantly, this research further informs survivorship care guidelines by highlighting specific high-risk groups which may require additional screening and monitoring as well as interventions to reduce the burden of comorbidities and improve long-term survival. This research also informs the design of future cancer survivorship studies, which should incorporate a cancer-free comparison, start at time of diagnosis, and include both pre- and post-menopausal women. Collectively, these findings support a tailored approach for treatment and prevention strategies to continue to improve the long-term prognosis after breast cancer.

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Chapter 7. Curriculum vitae

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EDUCATION

2014-	PhD	Epidemiology, Johns Hopkins University Advisor: Kala Visvanathan, MD, MHS, FRACP
2011-2013	SM	Epidemiology, Harvard University Thesis: Chronotype and breast cancer risk in a cohort of U.S. nurses
2003-2007	BA	Sociology and Anthropology, Lewis and Clark College

PROFESSIONAL EXPERIENCE

2016-Present	**Graduate Research Assistant**, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD Supervisor: Kala Visvanathan, MD, MHS, FRACP
2014-2015	**Graduate Research Assistant**, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD Supervisor: Anne Rositch, PhD
2013-2014	**Statistician**, Brigham and Women's Hospital, Channing Laboratory, Boston, MA Supervisors: Eva Schernhammer, DrPH, MD; Olivia Okereke, MD, MS
2009-2011	**Project Assistant II**, Cancer Prevention Institute of California, Fremont, CA Supervisor: Enid Santarino, MPH
2009	**Research Intern,** University of California, San Francisco, San Francisco, CA Supervisor: Carmen Masson, PhD
2009	**Research Intern,** University of California, Berkeley, Berkeley, CA Supervisor: Perfecto Munoz, MA, MPH
2007-2009	**Content Coordinator**, Mutualart.com, New York, NY

HONORS AND AWARDS

2016	Carol Martin Eliasberg Scholarship in Cancer Prevention Johns Hopkins Bloomberg School of Public Health

2016 Jean Coombs Award
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

2015-2018 Cancer Epidemiology, Prevention and Control Training Fellowship
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

MEMBERSHIPS

American Association for Cancer Research, Associate Member, 2016-2018
Society for Epidemiologic Research, Student Member, 2016-2018

BIBLIOGRAPHY

Peer-reviewed research papers

1. **Ramin, C.,** May, BJ., Roden, RBS., Petry, D., Armstrong, DK., Visvanathan, K. (*Submitted).* Evaluation of bone health in breast cancer survivors compared to cancer-free women: A prospective study within a young familial risk cohort.

2. **Ramin, C.**, Wang, W., Prescott, J., Rosner, B., Simon, NM., De Vivo, I., Okereke, OI. A prospective study of leukocyte telomere length and risk of phobic anxiety among women. *Psychiatry Research.* 230:2 2015.

3. Vetter, C., Devore, E., **Ramin, C**., Speizer, F., Willett, W., Schernhammer, E. Mismatch of sleep and work timing and risk of type 2 diabetes. *Diabetes Care.* 38:9 2015.

4. **Ramin, C**., Massa, J., Wegrzyn, LR., Devore, E., Pierre-Paul, J., Schernhammer, E. The association of body size in early to mid-life with adult urinary 6-sulfatoxymelatonin levels among night shift health care workers. *BMC Public Health*. 72:2 2015.

5. Devore, E., Kim, S., **Ramin, C**., Wegryzn, LR., Mass, JL., Holmes, M., Michels, KB., Tamimi, RM., Forman, JP., Schernhammer, E. Antihypertensive medication use and incident breast cancer among women. *Breast Cancer Research and Treatment.*150:1 2015.

6. **Ramin, C**., Devore, E., Wang, W., Wegrzyn, L., Schernhammer, E. Rotating night shift work at specific age ranges and correlations with chronic disease risk factors. *Occupational and Environmental Medicine*. 15:1 2015.

7. **Ramin, C**., Devore, E., Pierre-Paul, J., Duffy, JF., Hankinson, SE., Schernhammer, E. Chronotype and breast cancer risk in a cohort of U.S. nurses. *Chronobiology International.* 30:9 2013.

Poster presentations

Ramin, C., May, BJ., Roden, RBS., Petry, D., Armstrong, DK., Visvanathan, K. Evaluation of bone health in breast cancer survivors compared to cancer-free women: A prospective study within a young familial risk cohort. Annual Meeting of the American Association for Cancer Research. Washington, DC; 2017 April.

TEACHING

Guest lecturer

2016-2017 Clinical Aspects of Reproductive Health, Department of Population, Family and Reproductive Health, Johns Hopkins University
Title: "Epidemiology of Breast and Ovarian Cancer"

Teaching assistant

2016 Teaching Assistant, Epidemiologic Methods 3
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
Instructors: Keri Althoff, PhD; David Dowdy, PhD

2015 Teaching Assistant, Principles of Epidemiology
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
Instructor: Rosa Crum, MD

Tutor

2016 Epidemiologic Methods
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health

PROFESSIONAL ACTIVITIES

2016-2017 Co-coordinator, Cancer Epidemiology, Prevention, and Control Research in Progress

2015-2016 Lead co-coordinator, Cancer Epidemiology, Prevention, and Control Journal Club

SERVICE

Peer reviewer for journals

Cancer Causes & Control
British Journal of Cancer
Occupational and Environmental Medicine
PLoS One